Delacroix-Muirheid


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key terms
Query 1
Cetrorelix

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=> e cetrorelix/cn 5
E1            1     CETRIMS/CN
E2            1     CETRIPS/CN
E3            1 --> CETRORELIX/CN
E4            1     CETYL .BETA.-AMINOCROTONATE/CN
E5            1     CETYL .GAMMA.-AMINOBUTYRATE/CN

=> s e3; fil ca,caplus
L1            1 CETRORELIX/CN


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=> s l1 or cetrorelix
L2           61 FILE CA
L3           66 FILE CAPLUS

TOTAL FOR ALL FILES
L4          127 L1 OR CETRORELIX

=> s l4 and (fertil? or infertil? or ovar? or reproduct? or reprod##)
L5           19 FILE CA
L6           22 FILE CAPLUS

TOTAL FOR ALL FILES
L7           41 L4 AND (FERTIL? OR INFERTIL? OR OVAR? OR REPRODUCT? OR REP
                ROD##)

=> s l4 and ovulat?
L8            8 FILE CA
L9            8 FILE CAPLUS

TOTAL FOR ALL FILES
L10          16 L4 AND OVULAT?

=> s l10 or l7
L11          22 FILE CA
L12          25 FILE CAPLUS
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TOTAL FOR ALL FILES
L13 47 L10 OR L7

=> s l13 and admin?
L14 15 FILE CA
L15 16 FILE CAPLUS

TOTAL FOR ALL FILES
L16 31 L13 AND ADMIN?

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PROCESSING COMPLETED FOR L16
L17 16 DUP REM L16 (15 DUPLICATES REMOVED)

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biosi,medl,embas,lifesci,biotechd,wpid,confsci,dissabs,scisearch,jicst,promt,toxlit,toxlin

L17 ANSWER 1 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 1
AN 127:140580 CA
TI Combination of LH-RH analogs and antiestrogens for treatment of gynecological disorders
IN Stoeckemann, Klaus; Muhn, Peter
PA Schering A.-G., Germany
SO Ger. Offen., 5 pp.
CODEN: GWXXBX
PI DE 19604231 A1 970731
AI DE 96-19604231 960129
DT Patent
LA German
AB Combinations of LH-RH analogs and antiestrogens with tissue-selective estrogenic activity are useful for treatment of gynecol. disorders, esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium as a model of endometriosis, the LH-RH antagonist antide (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to a redn. in endogenous estrogen level resembling that occurring after **ovariectomy**, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen raloxifen (3 mg/day orally) was also **administered** during the period of antide **administration**, the endometriosis regressed but no decrease in estrogen level occurred.
IT **120287-85-6, Cetrorelix**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of LH-RH analogs and antiestrogens for treatment of gynecol. disorders)

L17 ANSWER 2 OF 16 CAPLUS COPYRIGHT 1997 ACS
AN 1997:554033 CAPLUS
TI Lhrh-antagonists in the treatment of **fertility** disorders
IN Engel, Juergen Prof Dr; Bouchard, Philippe Bouchard; Frydman, Rene Prof Dr; Diedrich, Klaus Prof Dr; Devroey, Paul Prof Dr
PA Asta Medica Aktiengesellschaft, Germany
SO Eur. Pat. Appl., 4 pp.
CODEN: EPXXDW
PI EP 788799 A2 970813
DS R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 97-100852 970121

PRAI US 96-11282 960207
DT Patent
LA English
AB This inventions relates to the prepn. of a medicament to be applied in the field of treating **infertility** disorders with or without assisted **reprodn**. techniques. In particular the improvement is directed to use an LH-RH Antagonist preferably **Cetrorelix** for prepn. of an medicament applied in the method of treating **infertility** disorders by inducing follicle growth by **administration** of exogenous gonadotropins and in **administering** the LH-RH Antagonist which contains an amt. of LH-RH Antagonist as low as only to suppress endogenous LH but the FSH secretion is maintained at a natural level and the individual estrogen development is not affected. When using the prepn., the follicle development must not be in each case externally stimulated (e.g. by the addn. of gonadotropins) but can be maintened by endogenous gonadotropins. Advantageously the prepn. can be given in the range of 0.1 to 5 mg of **Cetrorelix**/day during a multiple dosing posoilogy.

L17 ANSWER 3 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 126:55018 CA
TI Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal gonadotropin and gonadotropin-releasing hormone antagonist (**Cetrorelix**)
AU Albano, C.; Smitz, J.; Camus, M.; Riethmuller-Winzen, H.; Siebert-Weigel, M.; Diedrich, K.; Van Steirteghem, A.C.; Devroey, P.
CS Centre for Reproductive Medicine, University Hospital and Medical School, Dutch-speaking Brussels Free University, Brussels, 1090, Belg.
SO Hum. Reprod. (1996), 11(10), 2114-2118
CODEN: HUREEE; ISSN: 0268-1161
PB Oxford University Press
DT Journal
LA English
AB A third-generation gonadotrophin-releasing hormone antagonist (**Cetrorelix**) was used during **ovarian** stimulation in 32 patients undergoing assisted **reprodn**., to prevent the premature LH surge. In all patients, **ovarian** stimulation was carried out with two or three ampoules of human menopausal gonadotrophin (HMG), starting on day 2 of the menstrual cycle. In addn., 0.5 mg of **Cetrorelix** was **administered** daily from day 6 of HMG treatment until the day of **ovulation** induction by human chorionic gonadotropin (HCG). A significant drop in plasma LH concn. was obsd. within a few hours of the first **administration** of **Cetrorelix**. Moreover, no LH surge was detected at any point in the treatment period in any of the 32 patients. A mean estradiol concn. of 2122.+-.935 ng/l was obsd. on the day of the HCG **administration**, indicating normal folliculogenesis. Like LH, progesterone concn. also dropped within a few hours of the first **administration** of **Cetrorelix**. A 0.5 mg daily dose of **Cetrorelix** prevented a premature LH surge in all the 32 patients treated.
IT **120287-85-6, Cetrorelix**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hormonal profile during follicular phase in cycles stimulated with menopausal gonadotropin and LH-RH antagonist **Cetrorelix**)

L17 ANSWER 4 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 125:238855 CA
TI Subtle progesterone rise after the **administration** of the gonadotropin-releasing hormone antagonist **Cetrorelix** in intracytoplasmic sperm injection cycles
AU Ubaldi, Filippo; Albano, Carola; Peukert, Manfred; Riethmuller-Winzen, Hilde; Camus, Michel; Smitz, Johan; Van Steirteghem, Andre; Devroey, Paul
CS Centre Reproductive Medicine, Dutch-speaking Brussels Free University, Brussels, Belg.
SO Hum. Reprod. (1996), 11(7), 1405-1407
CODEN: HUREEE; ISSN: 0268-1161
DT Journal
LA English
AB In the present study, subtle serum progesterone rise (.gtoreq.1.1 ng/mL) during the late follicular phase is reported, for the first time to our knowledge, in patients using a potent gonadotropin-releasing hormone (GnRH) antagonist, **Cetrorelix**, in combination with human menopausal gonadotropin (HMG) for **ovarian** stimulation prior to intracytoplasmic sperm injection (ICSI). In five out of 24 patients (20%) serum progesterone levels were .gtoreq.1.1 ng/mL. The cycle characteristics of the patients were similar in both groups. No premature endogenous LH surge occurred and the serum LH concns. were constantly low during the follicular phase. The estradiol and FSH exposure were higher in cycles with premature luteinization. The greater estradiol and FSH exposure confirm that one of the possible factors inducing subtle serum progesterone rise is the increased estradiol and FSH-induced LH receptivity in granulosa cells.
IT **120287-85-6**, **Cetrorelix**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(progesterone increase in blood serum during **Cetrorelix** therapy with gonadotropins in women)

L17 ANSWER 5 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 4
AN 124:21841 CA
TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview
AU Reissmann, Th.; Felberbaum, R.; Diedrich, K.; Engel, J.; Comaru-Schally, A. M.; Schally, A. V.
CS ASTA Medica AG, Frankfurt/Main, Germany
SO Hum. Reprod. (1995), 10(8), 1974-81
CODEN: HUREEE; ISSN: 0268-1161
DT Journal; General Review
LA English
AB A review with 62 refs. LH-releasing hormone (LHRH) plays a crucial role in controlling the **ovarian** cycle in women. By modification of the mol. structure of this decapeptide, analogs were synthesized with agonistic or antagonistic effects on the gonadotropic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ("flare up"), lead to desensitization of the gonadotropic cells and a redn. in the no. of LHRH receptors on the cell membrane ("down-regulation"), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After **administration** of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ("pituitary response") after pretreatment with an

antagonist. This different pharmacol. mechanism of LHRH antagonists makes possible new approaches to **ovarian** stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted **reprodn**. technol. (ART) programs, can be abolished by short term application of an LHRH antagonist assocd. with a reduced human menopausal gonadotrophin (HMG) requirement for **ovarian** stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and **ovulation** induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, esp. **Cetrorelix** which is presently used clin. in controlled phase II clin. studies.

L17 ANSWER 6 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 5
AN 122:282455 CA
TI Evaluation of the in vitro and in vivo activity of the L-, D,L- and D-Cit6 forms of the LH-RH antagonist **Cetrorelix** (SB-75)
AU Pinski, J.; Schally, A. V.; Yano, T.; Groot, K.; Srkalovic, G.; Serfozo, P.; Reissmann, T.; Bernd, M.; Deger, W.; et al.
CS Polypeptide Cancer Inst., VA Med. Cent., New Orleans, LA, USA
SO Int. J. Pept. Protein Res. (1995), 45(5), 410-17
CODEN: IJPPC3; ISSN: 0367-8377
DT Journal
LA English
AB The objective of this study was to examine the in vivo and in vitro gonadotropin-inhibiting potencies, edematogenic activities and the receptor binding affinities of the D-Cit6, and L-Cit6 forms of the LH-RH antagonist **Cetrorelix**. To demonstrate the suppressive effects of two different diastereomers of SB-75 and their racemic mixt. on LH and FSH release, [D-Cit6] SB-75 was injected s.c. in doses of 2.5 and 10 .mu.g/rat, [DL-Cit6]-SB-75 in doses of 5 and 20 .mu.g/rat and [L-Cit6]-SB-75 in doses of 12.5 and 50 .mu.g/rat to castrated male rats. Two hours after **administration**, there was no difference in LH levels between rats injected with the L-form and control animals, indicating a low activity and(or) a rapid enzymic degrdn. of this peptide. The (1:1) diastereomeric mixt. was only about half as potent in suppression in LH release compared to [D-Cit6]-SB-75. Serum FSH levels were suppressed for more than 48 h after the **administration** of 10 .mu.g [D-Cit6]-SB-75 and 20 .mu.g of [DL-Cit6]-SB-75, resp. [D-Cit6]-SB-75 **administered** at a dose of 2 .mu.g/rat induced 100% inhibition of **ovulation**, while 4 .mu.g/rat of the DL-Cit6 peptide were necessary to produce the same effect. [L-Cit6]-SB-75 given at a high dose of 40 .mu.g/rat produced only 14% inhibition of **ovulation**. The D-Cit6 form of SB-75 produced skin lesions with a much smaller diam. than the L-isomer, and was about 34 times less edematogenic. [D-Cit6]-SB-75 was bound more powerfully to high-affinity pituitary LH-RH receptors than either DL-Cit6 or L-Cit6 analogs. In vitro assays based on the superfusion of dispersed rat pituitary cells on a column, followed by RIA for LH, also demonstrated a lower inhibitory activity for the L-Cit6 analog, but the differences between D-, DL- and L-citrulline analogs were smaller than in vivo. The results indicate that the LH-RH antagonist [D-Cit6]-SB-75 is more effective in suppression of gonadotropin release in vivo and in vitro, less edematogenic and possesses higher binding affinity to pituitary LH-RH receptors than the DL- and L-citrulline decapeptide analogs.

IT **120287-85-6**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure-activity evaluation of L-, DL- and D-citrulline forms of LH-RH antagonist **Cetrorelix**)

L17 ANSWER 7 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 6
AN 123:132826 CA
TI Preserved pituitary response under **ovarian** stimulation with HMG and GnRH antagonists (**Cetrorelix**) in women with tubal **infertility**
AU Felberbaum, Ricardo E.; Reissmann, Thomas; Kuepker, Wolfgang; Bauer, Otmar; Hasani, Safaa Al; Diedrich, Christa; Diedrich, Klaus
CS Department of Obstetrics an Gynecology, Medical University of Luebeck, Luebeck, Germany
SO Eur. J. Obstet. Gynecol. Reprod. Biol. (1995), 61(2), 151-5
CODEN: EOGRAL; ISSN: 0301-2115
DT Journal
LA English
AB To examine the pituitary response in patients undergoing short-term application of the GnRH antagonist **Cetrorelix** in the mid-cycle phase for hypophysial suppression of premature LH surges within an IVF-program. Twenty patients suffering from primary or secondary tubal **infertility** were stimulated with HMG from cycle day 2. From day 7 till **ovulation** induction **Cetrorelix** was **administered** in two different dose regimens (15 patients 3 mg s.c. daily; 5 patients 1 mg s.c. daily). Three hours before **ovulation** induction a GnRH test was performed using 25 .mu.g of native GnRH and the pituitary response examd. by measurement of the serum LH concn. after 30 min. Premature LH surges could be avoided in the 3-mg group and in the 1-mg group, resp. Due to this, none of the cycles had to be cancelled. Estradiol profiles and ultrasound demonstrated a satisfactory follicular maturation. All patients showed pronounced suppression of the serum LH levels before **ovulation** induction. The mean increase of serum LH due to the performed GnRH test was 10 mIU/mL for the 3-mg group, while the av. max. in the 1-mg group was about 32.5 mIU/mL. The pituitary response is preserved by the treatment with the GnRH antagonist **Cetrorelix**. The extent of suppression of the adenohypophysis, as expressed by the different reactions on GnRH test, can be modulated by the dosage **administered**. This should allow **ovulation** by GnRH or one of its agonists instead of hCG, which could be beneficial in patients at high risk of **Ovarian** Hyperstimulation Syndrome (OHSS) and those suffering from Polycystic **Ovary** Disease (PCOD).
IT **120287-85-6, Cetrorelix**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preserved pituitary response under **ovarian** stimulation with HMG and GnRH antagonists (**Cetrorelix**) in women with tubal **infertility**)

L17 ANSWER 8 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 7
AN 123:47250 CA
TI Pharmacological influence on the **fertility** in man
AU Neye, Holger
CS Muenster, Germany
SO Dtsch. Apoth. Ztg. (1995), 135(8), 39-40, 42

CODEN: DAZEA2; ISSN: 0011-9857
DT Journal; General Review
LA German
AB A review, with 7 refs., on the hormonal contraception in males by suppressing FSH, LH, and intratesticular testosterone and a simultaneous substitution of extratesticular testosterone. A combined **administration** of gonadorelin antagonist **cetrorelix** with 19-nortestosterone induces a complex a complete azospermia without side effects.

L17 ANSWER 9 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 8
AN 121:99269 CA
TI Inhibition of growth of OV-1063 human epithelial **ovarian** cancer xenografts in nude mice by treatment with luteinizing hormone-releasing hormone antagonist SB-75
AU Yano, Tetsu; Pinski, Jacek; Halmos, Gabor; Szepeshazi, Karoly; Groot, Kate; Schally, Andrew V.
CS Cancer Inst., Veterans Affairs Med. Center, New Orleans, LA, 70146, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(15), 7090-4
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Female athymic nude mice bearing xenografts of OV-1063 human epithelial **ovarian** cancer cell line were treated with potent LH (LH)-releasing hormone (LH-RH) antagonist Sb-75 { **Cetrorelix**; [Ac-D-NMal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]LH-RH in which Ac-D-Nal(2) = N-acetyl-3-(2-naphthyl)-D-alanine, D-Phe(4CI) = 4-chloro-D-phenylalanine, D-Pal(3) = 3-(3-pyridyl)-D-alanine, and D-Cit = D-Citrulline} or with the agonist [D-Trp6]LH.RH. In the first expt., SB-75 and [D-Trp6]LH-RH were **administered** in the form of microcapsules releasing 60 and 25 .mu.g/day, resp. In the second study, the analogs were given by daily s.c. injections in doses of 100 mg/day. In both expts., tumor growth, as measured by redn. in tumor vol., percentage change in tumor vol., tumor burden, and increase in tumor doubling time, was significantly inhibited by treatment with SB-75 but not with [D-Trp6]LH-RH. Uterine and **ovarian** wts. were reduced and serum LH levels decreased by **administration** of either analog. Chronic treatment with SB-75 greatly reduced the concn. of receptors for epidermal growth factor and insulin-like growth factor I in tumor cell membranes, a phenomenon that might be related to tumor growth inhibition. It is possible that the antitumoral effects of SB-75 on OV-1063 **ovarian** cancers are exerted not only through the suppression of the pituitary-gonadal axis, but also directly. In view of its strong inhibitory effect on the growth of OV-1063 **ovarian** cancers in vivo, the potent LH-RH antagonist SB-75 might be considered for possible hormonal therapy of advanced epithelial **ovarian** carcinoma.

L17 ANSWER 10 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 9
AN 125:722 CA
TI Persistent blockade of the pituitary gonadal axis in patients with prostatic cancer by the LH-RH antagonist SB-75 (**Cetrorelix**)
AU Gonzalez-Barcena, D.; Vadillo-Buenfil, M.; Cortez-Morales, A.; Romero, M. A.; Engel, J.; Comaru-Schally, A. M.; Schally, A. V.; Reissman, Th.
CS Hosp. Esp. C.M.R., IMSS, Mexico City, Mex.
SO Proc. Int. Cancer Congr., Free Pap. Posters, 16th (1994), Volume 3,

2201-2204. Editor(s): Rao, R. S. Publisher: Monduzzi Editore, Bologna, Italy.
CODEN: 62UYAO
DT Conference
LA English
AB Our objective was to use the LH-RH analog SB-75, **Cetrorelix** to treat a group of patients with advanced prostrate carcinoma. The antagonists SB-75 was well tolerated. No local or systemic effects were obsd. These results show that the chronic **administration** of the LH-RH antagonists SB-75, **Cetrorelix** is an effective therapy for the management of advanced prostate cancer.

L17 ANSWER 11 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 10
AN 121:50450 CA
TI Inhibitory effect of bombesin/gastrin-releasing peptide antagonist RC-3095 and luteinizing hormone-releasing hormone antagonist SB-75 on the growth of MCF-7 MIII human breast cancer xenografts in athymic nude mice
AU Yano, Tetsu; Pinski, Jacek; Szepeshazi, Karoly; Halmos, Gabor; Radulovic, Sinisa; Groot, Kate; Schally, Andrew V.
CS Veterans Aff. Med. Cent., Endocr. Polypept. and Cancer Inst., New Orleans, LA, USA
SO Cancer (Philadelphia) (1994), 73(4), 1229-38
CODEN: CANCAR; ISSN: 0008-543X
DT Journal
LA English
AB The results of several clin. trials using various LH-releasing hormone agonists for treatment of advanced breast cancer are encouraging. However, only about 30% of breast cancers are estrogen-dependent and can be treated by hormonal manipulation. New therapeutic approaches combining estrogen ablation therapy with other compds. must be explored. Various studies suggest that bombesin or gastrin-releasing peptide acts as an autocrine growth factor and may play a role in the initiation and progression of some cancers, including that of the breast. Female athymic nude mice bearing xenografts of the MCF-7 MIII human breast cancer cell line were treated for 7 wk with bombesin/gastrin-releasing peptide antagonist (D-Tpi6, Leu13 .PSI.[CH2NH]-Leu14) bombesin (6-14) (RC-3095) injected s.c. daily at a dose of 20 .mu.g and LH-releasing hormone antagonist SB-75 (**Cetrorelix**) **administered** biweekly in the form of microgranules releasing 45 .mu.g/day. After 2 wk of treatment, a significant inhibition of tumor vol. was obsd. in the groups treated with RC-3095 alone or in combination with SB-75 but not in those treated with SB-75 as a single agent. After 7 wk, tumor growth as measured by tumor vol. and percentage changes in tumor vol. and tumor wt. was greatly inhibited in all of the treated groups. Uterine and **ovarian** wts. were reduced and serum LH levels decreased by **administration** of SB-75 alone or in combination with RC-3095. Histol., a significant decrease in argyrophilic nucleolar organizer region count in tumor cell nuclei was obsd. in all of the treated groups, indicating a lower proliferation of these cells. High-affinity binding sites for bombesin were detected in cultured MCF-7 MIII cells. Chronic treatment with RC-3095 caused a significant down-regulation of epidermal growth factor receptors in tumor cell membranes, which might be related to tumor inhibition. In studies in vitro, SB-75 inhibited proliferation of MCF-7 cells in culture but not proliferation of MCF-7 MIII cells. Because previously the authors demonstrated that RC-3095 inhibits the proliferation of MCF-7 MIII

cells in vitro, it appears that the major antitumoral effect of RC-3095 on the MCF-7 MIII cancer line is direct, whereas that of SB-75 is indirect, and that it is mediated by suppression of the pituitary-gonadal axis. In view of its immediate and powerful inhibitory effect on MCF-7 MIII tumors, bombesin/gastrin-releasing peptide antagonist RC-3095 might be considered as a possible new agent for the treatment of breast cancer.

L17 ANSWER 12 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 11
AN 121:293153 CA
TI Treatment with luteinizing hormone-releasing hormone antagonist SB-75 decreases levels of epidermal growth factor receptor and its mRNA in OV-1063 human epithelial **ovarian** cancer xenografts in nude mice
AU Shirahige, Yutaka; Cook, Curtiss B.; Pinski, Jacek; Halmos, Gabor; Nair, Radha; Schally, Andrew V.
CS Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SO Int. J. Oncol. (1994), 5(5), 1031-5
CODEN: IJONES; ISSN: 1019-6439
DT Journal
LA English
AB The aim of this study was to investigate the effect of **administration** of LH-RH antagonist SB-75 and agonist [D-Trp6]LH-RH on receptors for epidermal growth factor (EGF) in OV-1063 human epithelial **ovarian** cancer. Female athymic nude mice bearing xenografts of OV-1063 human epithelial **ovarian** cancer were treated for 3 wk with the modern LH-releasing hormone (LH-RH) antagonist [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10] LH-RH (SB-75, **Cetrorelix**), the agonist [D-Trp6]LH-RH, or bombesin/gastrin-releasing peptide antagonist RC-3095. SB-75 and [D-Trp6] LH-RH were injected s.c. at doses of 100 .mu.g/day, and RC-3095 was injected at a dose of 40 .mu.g/day. Tumor growth, as measured by percentage change in tumor vol., was significantly inhibited by the treatment with SB-75, but not by [D-Trp6] LH-RH or RC-3095. Treatment with SB-75 greatly decreased the levels of mRNA for EGF receptor and reduced the no. of EGF binding sites on tumor membranes. Effects of SB-75 on EGF receptors might be related to inhibition of tumor growth. The authors findings support the view that LH-RH antagonists such as SB-75 could be considered for possible hormonal therapy of epithelial **ovarian** cancer.

L17 ANSWER 13 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 12
AN 121:293123 CA
TI Seven-day **administration** of the gonadotropin-releasing hormone antagonist **Cetrorelix** in normal cycling women
AU Sommer, Lieselotte; Zanger, Kerstin; Dyong, Thomas; Dorn, Christoph; Luckhaus, Johannes; Diedrich, Klaus; Klingmuller, Dietrich
CS Dep. Clinical Biochemistry Clinical Hosp. Gynecology Obstretics, Univ. Bonn, Germany
SO Eur. J. Endocrinol. (1994), 131(3), 280-5
CODEN: EJOEEP; ISSN: 0804-4643
DT Journal
LA English
AB In contrast to gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists do not show any stimulatory effect on the pituitary but their clin. usage was precluded by severe side effects and high dose requirements. The authors report here on a 7-day treatment using the potent GnRH antagonist **Cetrorelix** ([Ac-D-Nal(2)1,D-

Phe(4Cl)2,D-Pal(3)3,D-Cit6,D-Ala10]GnRH) on five women 23-33 yr old. All women were **ovulatory** and were studied during three consecutive cycles; a control cycle, a treatment cycle and a post-treatment control cycle. Throughout the control cycles blood samples were obtained daily during cycle days 8-18 and on days 21 and 23 during the remainder of the control cycles. On the eighth day of the treatment cycle women were hospitalized at 07.00 h for 26 h. Repeated blood samples were drawn at 15-min intervals during the entire period. Subjects received 3 mg of **Cetrorelix** s.c. for the first time at 09.00 h on the eighth day of the cycle and daily at 08.00 h for the following 6 days. Blood samples were obtained daily over a period of 25 days and every third day throughout the remainder of the treatment cycle. Twenty-four hours after the first application of **Cetrorelix**, LH and estradiol were in the subnormal range and remained subnormal until the end of medication. The suppressive effect of **Cetrorelix** compared to pretreatment values lasted at least 6 days for LH and FSH and 11 days after the last **Cetrorelix** compared to pretreatment values lasted at least 6 days for LH and FSH and 11 days after the last **Cetrorelix** injection for estradiol. An LH surge followed by postovulatory progesterone values was found 22.6 days after the last injection. During application of the GnRH antagonist, LH was reduced to 16.1%, FSH to 58.7% and estradiol to 17.9% compared to the individual pretreatment values. The consecutive cycle after completion of treatment was comparable to the length of the pretreatment cycle. No serious side effects were obsd. In summary, the results of this study give evidence of the effectiveness and safety of this new GnRH antagonist used in low dosages for possible therapeutic application in sex-hormone-dependent diseases in women.

IT **120287-85-6**, **Cetrorelix**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(seven-day **administration** of gonadotropin-releasing hormone antagonist **Cetrorelix** in normal cycling women)

L17 ANSWER 14 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 13
AN 120:96364 CA
TI Recovery of pituitary-gonadal function in male rats after long-term suppression induced by a single injection of microcapsules of LH-RH antagonist **cetrorelix** (SB-75)
AU Pinski, Jacek; Yano, Tetsu; Szepeshazi, Karoly; Groot, Kate; Schally, Andrew V.
CS Endocr., Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SO J. Androl. (1993), 14(3), 164-9
CODEN: JOAND3; ISSN: 0196-3635
DT Journal
LA English
AB The clin. utility of LH-releasing hormone (LH-RH) analogs can be greatly enhanced by a sustained delivery system, which can maintain elevated peptide levels in the blood for prolonged periods of time, up to several weeks. Recently, the authors developed long-acting microcapsules and microgranules of the LH-RH antagonist SB-75. In this study, the authors examd. the suppressive effects of a single injection of microcapsules of antagonist SB-75 on gonadotropin and testosterone secretion, as well as on **fertility**, in male rats and on the reversibility of those effects. Serum SB-75 levels were measured by RIA. A dose of 20 mg of microcapsules/rat contg. 3.58 mg of antagonist in poly(D,L-lactide-co-glycolide), **administered** i.m., produced SB-75 levels higher than 20

ng/mL for approx. 24 days, and a significant elevation was maintained until day 90. Serum testosterone was decreased to castration values for 164 days and LH levels were suppressed below the detection limit of the RIA for a period of 102 days. Serum FSH was suppressed by more than 90%, as compared with control animals, for a period of 58 days and remained significantly decreased until day 164 after the injection. This treatment also caused a significant decrease in the wts. of the testes, seminal vesicles, and ventral prostate 30 days after peptide **administration**. The histol. of the testes from the treated rats showed that spermatogenesis was totally depressed. No mature elongated or round spermatids were found in the seminiferous tubules, with spermatocytes being the most advanced germ cell form in 99.5% of the testicular tubules. Ten months after injection, complete recoveries in organ wts., hormonal levels, and **fertility** were obsd. Histol. studies revealed a complete recovery of spermatogenesis, with 100% of seminiferous tubules contg. mature elongated spermatids. All treated rats were able to impregnate normal female rats. The offspring were normal, with no evidence of genetic abnormalities. The overall results demonstrate the efficacy of SB-75 microcapsules in suppressing the pituitary-gonadal axis for a prolonged period of time, and they also show that the long-term suppression of gonadal function induced by chronic treatment with antagonist SB-75 is completely reversible.

L17 ANSWER 15 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 14
AN 112:192215 CA
TI Growth inhibition of mouse MXT mammary tumor by the luteinizing hormone-releasing hormone antagonist SB-75
AU Szende, Bela; Srkalovic, Gordan; Groot, Kate; Lapis, Karoly; Schally, Andrew V.
CS Endocrine, Polypept. Cancer Inst., Veterans Adm. Med. Cent., New Orleans, LA, 70146, USA
SO J. Natl. Cancer Inst. (1990), 82(6), 513-17
CODEN: JNCIEQ; ISSN: 0027-8874
DT Journal
LA English
AB Female BDF1 mice bearing MXT mammary adenocarcinomas were treated for 3 wk with the LH-RH antagonist [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]-LH-RH (SB-75), with the agonist D-Trp6-LH-RH, with tamoxifen (5 .mu.g/animal/day, s.c.), with the combination of D-Trp6-LH-RH and tamoxifen, or by surgical **ovariectomy**. SB-75 and D-Trp6-LH-RH were **administered** in the form of microcapsules releasing 25 .mu.g/day. The redn. in tumor wts. after treatment with SB-75, D-Trp6-LH-RH, D-Trp6-LH-RH plus tamoxifen, or **ovariectomy** was 84%, 64%, 33%, or 67%, resp. Tamoxifen alone was ineffective. Histol., the regressive changes in the treated tumors were characteristic of apoptosis (programmed cell death). Its potency and its immediate inhibitory effect suggested that the LH-RH anatgonist SB-75 should be considered as a possible hormonal agent for the treatment of breast cancer.
IT **126299-94-3**
RL: BIOL (Biological study)
(mammary tumor growth inhibition by)

L17 ANSWER 16 OF 16 CA COPYRIGHT 1997 ACS DUPLICATE 15
AN 112:172406 CA
TI Development of radioimmunoassay for a potent luteinizing hormone-releasing hormone antagonist. Evaluation of serum levels

after injection of [Ac-3-(2-naphthyl)-D-Ala1, D-Phe(pCl)2, 3-(3-pyridyl)-D-Ala3, D-Cit6, D-Ala10] LHRH

AU Csernus, V. J.; Szende, B.; Groot, K.; Redding, T. W.; Schally, A. V.

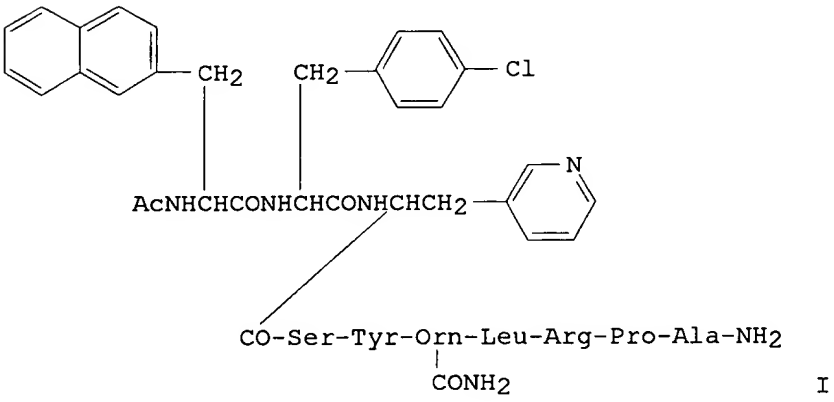
CS VA Med. Cent., Endocr. Polypept. Cancer Inst., New Orleans, LA, 70146, USA

SO Arzneim.-Forsch. (1990), 40(2), 111-18
CODEN: ARZNAD; ISSN: 0004-4172

DT Journal

LA English

GI



I

AB To facilitate pharmacokinetic studies necessary for exptl. and clin. investigation of the title LH-RH analog (SB-75; I) a highly sensitive and specific RIA was developed. The antibody against SB-75 was generated in rabbits. No cross-reactions were detected with several natural peptides and analogs. The sensitivity of the assay is 0.6 pg/tube. The RIA is suitable for direct detn. of SB-75 in 20 .mu.L serum. Two lots of SB-75 microcapsules exhibited different pharmacokinetic release patterns. Single i.m. injection of 20 mg SB-75 microcapsules, PLGA batch No. 001, into female rats maintained elevated serum SB-75 levels for 3 wk. The suppression of LH secretion during this period was indicated by histol. findings. The **ovaries** in the treated group were polyfollicular and no corpora lutea were present, indicating a prolonged **ovarian** inactivity due to LH deprivation. There was also a redn. in the size and wt. of the **ovaries** (40.4 mg vs. 66.7 mg for controls). The **administration** of SB-75 microcapsules, PLGA batch Nr. 002, to male rats produced high serum SB-75 levels for about 10 days, but an elevation in SB-75 values was maintained for 29 days. Serum testosterone (T), LH, and prolactin levels were reduced. A greater depression in serum T occurred on days 2-7, than on days 14-24, indicating that this batch exerted maximal effects during the 1st 7 days. Histol. examns. of the testicles revealed signs of impaired spermatogenesis. Prostate histol. in these rats also indicated reduced activity. Thus, improved sustained delivery formulations should be capable of maintaining therapeutic levels of the antagonist for several weeks. The RIA developed should be of value for monitoring SB-75 levels during long-term therapy.

IT **120287-85-6**, SB 75
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood serum by RIA)

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L19 32 FILE MEDLINE
L20 35 FILE EMBASE
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L21 3 FILE LIFESCI
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'CN' IS NOT A VALID FIELD CODE
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L24 0 FILE CONFSCI
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L27 0 FILE JICST-EPLUS
L28 6 FILE PROMT

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L30           6 FILE TOXLINE

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                ROD## OR OVULAT? OR GYNECOL?)

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L37           0 FILE WPIDS
L38           0 FILE CONFSCI
L39           0 FILE DISSABS
L40          19 FILE SCISEARCH
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L42           2 FILE PROMT
L43          13 FILE TOXLIT
L44           5 FILE TOXLINE

TOTAL FOR ALL FILES
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L46          41 DUP REM L45 (73 DUPLICATES REMOVED)

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L46  ANSWER 1 OF 41  BIOSIS  COPYRIGHT 1997 BIOSIS     DUPLICATE 1
AN  97:255861  BIOSIS
DN  99555064
TI  Comparison of different doses of gonadotropin-releasing hormone
    antagonist Cetrorelix during controlled ovarian
    hyperstimulation.
AU  Albano C; Riethmueller-Winzen H; Smitz J; Van Steirteghem A; Camus M;
    Devroey P
CS  Cent. Reprod. Med., Dutch-Speaking Brussels Free Univ., Laarbeeklaan
    101, B-1090 Brussels, Belgium
SO  Fertility and Sterility 67 (5). 1997.  917-922. ISSN: 0015-0282
LA  English
AB  Objective: To assess the minimal effective dose of a GnRH antagonist
    (Cetrorelix; Asta Medical, Frankfurt, Germany) to prevent
    premature LH surge in patients undergoing controlled ovarian
    hyperstimulation (COH) for assisted reproductive
    technologies. Design: In 69 patients COH was carried out with the
    association of hMG, starting on day 2 of the menstrual cycle, and a
    GnRH antagonist (Cetrorelix) was administered
    from day 6 of the hMG treatment (day 7 of the menstrual cycle) every
    day up to and including the last day of the hMG injection. In 32 and
    30 patients, 0.5 mg and 0.25 mg of Cetrorelix were
  administered, respectively. Seven patients received 0.1 mg of
  Cetrorelix. Setting: Tertiary referral center. Result(s): No
    premature endogenous LH surge occurred in patients treated with 0.5
    and 0.25 mg of Cetrorelix, and serum LH concentrations were
    maintained constantly low during the entire follicular phase in both
    groups. Follicle-stimulating hormone, LH, E-2, and P expressed as
    area under the curve were similar in both groups. A premature LH
```

surge (18 mIU/mL; conversion factor to SI unit, 1.00) with a concomitant P rise (1.7 mu-g/L; conversion factor to SI unit, 3.180) occurred in one of the seven patients treated with 0.1 mg **Cetrorelix**; therefore, treatment with this dose was discontinued. Conclusion(s): The minimal effective dose of **Cetrorelix** able to prevent premature LH surge in COH cycles is 0.25 mg **administered** daily.

L46 ANSWER 2 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 97197509 EMBASE
TI Pharmacological developments in male contraception.
AU Cosentino M.J.; Matlin S.A.
CS M.J. Cosentino, Department of Biology, Millersville University, Millersville, PA 17551, United States
SO Expert Opinion on Investigational Drugs, (1997) 6/6 (635-653). ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal
FS 010 Obstetrics and Gynecology
037 Drug Literature Index
LA English
SL English
AB To date, the current methods of male contraception are limited to condoms, coitus interruptus and vasectomy, all of which are beset with difficulties. The condom is inconvenient, dulls sensation, and although somewhat effective against sexually transmitted disease, has an increased failure rate over time of usage. Coitus interruptus reduces the pleasurable aspects of intercourse and is plagued with a high failure rate. Vasectomy is virtually sterilisation. The current research into new forms of contraception is as diverse as the mechanisms controlling male **fertility**. The majority of effort has focused on antispermatogenic agents. Hormonal agents that suppress spermatogenesis appear nearest to final development and are primarily centred around various testosterone esters. These can be **administered** alone or in combination with progestogens. Another promising line of study centres on gonadotropin releasing hormone (GnRH) antagonism resulting in suppression of gonadotropins. Nonhormonal antispermatogenic agents include numerous phytochemicals, and testicular enzyme inhibitors. Post-testicular approaches to male contraception include agents that interfere with sperm metabolism, motility, maturation or transport. This review summarises recent clinical and animal studies on these compounds with emphasis on their mechanism of action, advantages and drawbacks.

L46 ANSWER 3 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 2
AN 97:27788 BIOSIS
DN 99326991
TI Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal gonadotrophin and gonadotrophin-releasing hormone antagonist (**Cetrorelix**).
AU Albano C; Smitz J; Camus M; Riethmueller-Winzen H; Siebert-Weigel M; Diedrich K; Van Steirteghem A C; Devroey P
CS Centre Reproductive Med., Univ. Hosp. Med. Sch., Dutch-Speaking Brussels Free Univ., Laarbeeklaan 101, 1090 Brussels, Belgium
SO Human Reproduction (Oxford) 11 (10). 1996. 2114-2118. ISSN: 0268-1161
LA English
AB A third-generation gonadotrophin-releasing hormone antagonist (**Cetrorelix**) was used during **ovarian** stimulation in

32 patients undergoing assisted **reproduction**, in order to prevent the premature luteinizing hormone (LH) surge. In all patients, **ovarian** stimulation was carried out with two or three ampoules of human menopausal gonadotrophin (HMG), starting on day 2 of the menstrual cycle. In addition, 0.5 mg of **Cetrorelix** was **administered** daily from day 6 of HMG treatment until the day of **ovulation** induction by human chorionic gonadotrophin (HCG). A significant drop in plasma LH concentration was observed within a few hours of the first **administration** of **Cetrorelix** (P lt 0.005). Moreover, no LH surge was detected at any point in the treatment period in any of the 32 patients. A mean oestradiol concentration of 2122 +- 935 ng/l was observed on the day of the HCG **administration**, indicating normal folliculogenesis. Like LH, progesterone concentration also dropped within a few hours of the first **administration** of **Cetrorelix** (P lt 0.005). A 0.5 mg daily dose of **Cetrorelix** prevented a premature LH surge in all the 32 patients treated.

L46 ANSWER 4 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 3
AN 96:470098 BIOSIS
DN 99192454
TI Subtle progesterone rise after the **administration** of the gonadotrophin-releasing hormone antagonist **Cetrorelix** in intracytoplasmic sperm injection cycles.
AU Ubaldi F; Albano C; Peukert M; Riethmueller-Winzen H; Camus M; Smitz J; Van Steirteghem A; Devroey P
CS Centre Reproductive Med., Dutch-speaking Brussels Free Univ., Laarbeeklaan 101, B-1090 Brussels, Belgium
SO Human Reproduction (Oxford) 11 (7). 1996. 1405-1407. ISSN: 0268-1161
LA English
AB In the present study, subtle serum progesterone rise (gtoreq 1.1 ng/ml) during the late follicular phase is reported, for the first time to our knowledge, in patients using a potent gonadotrophin-releasing hormone (GnRH) antagonist, **Cetrorelix** , in combination with human menopausal gonadotrophin (HMG) for **ovarian** stimulation prior to intracytoplasmic sperm injection (ICSI). In five out of 24 patients (20%) serum progesterone levels were gtoreq 1.1 ng/ml. The cycle characteristics of the patients were similar in both groups. No premature endogenous luteinizing hormone (LH) surge occurred and the serum LH concentrations were constantly low during the follicular phase. The 17-beta oestradiol and follicle stimulating hormone (FSH) exposure were higher in cycles with premature luteinization. The greater oestradiol and FSH exposure confirm that one of the possible factors inducing subtle serum progesterone rise is the increased oestradiol and FSH-induced LH receptivity in granulosa cells.

L46 ANSWER 5 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 96138948 EMBASE
TI **Cetrorelix**.
SO Drugs of the Future, (1996) 21/3 (307-308).
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal
FS 010 Obstetrics and Gynecology
016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index

LA English

L46 ANSWER 6 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 4
AN 96:193227 BIOSIS
DN 98749356
TI Hormone profiles under **ovarian** stimulation with human menopausal gonadotropin (hMG) and concomitant **administration** of the gonadotropin releasing hormone (GnRH)-antagonist **cetrorelix** at different dosages.
AU Felberbaum R; Reissmann T; Kuepker W; Al-Hasani S; Bauer O; Schill T; Zoll C; Diedrich C; Diedrich K
CS Department Obstetrics Gynecology, Medical University Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany
SO Journal of Assisted Reproduction and Genetics 13 (3). 1996. 216-222. ISSN: 1058-0468
LA English
AB Purpose: The premature LH surge in ART programs seems to be avoided by daily **administration** of the GnRH-antagonist **Cetrorelix** during the midcycle phase in controlled **ovarian** hyperstimulation with hMG. The dosage necessary for sufficient suppression of the pituitary gland is not yet defined. Methods: To elucidate this question three daily dosages (3, 1, 0.5 mg) were **administered** and the hormone profiles obtained as well as the number of oocytes retrieved, the **fertilization** rate, and the consumption of HMG were compared. Results: No premature LH surge could be observed at any of the three dosages **administered** Both gonadotropins were deeply suppressed. The **fertilization** rates of the oocytes obtained were 45.3% in the 3-mg group, 53.1% in the 1-mg group, and 67.7% in the 0.5-mg group. The average uses of hMG ampoules were 30 in the 3-mg group, 27 in the 1-mg group, and 26 in the 0.5-mg group. Conclusions: Cetrolix, 0.5 mg/day, **administered** during the midcycle phase of controlled **ovarian** hyperstimulation with hMG is enough to prevent completely the premature LH surge. Perhaps even lower dosages would be sufficient. Regarding **fertilization** rates and use of hMG, the lower dosage seems to be the most favorable.

L46 ANSWER 7 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 96194150 EMBASE
TI Triggering of **ovulation** by a gonadotropin-releasing hormone (GnRH) agonist in patients pretreated with a GnRH antagonist.
AU Olivennes F.; Fanchin R.; Bouchard P.; Taieb J.; Frydman R.
CS Department of Obstetrics/Gynecology, Antoine Beclere Hospital, 157, Rue de la porte de Trivaux, 92140 Clamart, France
SO Fertility and Sterility, (1996) 66/1 (151-153). ISSN: 0015-0282 CODEN: FESTAS
CY United States
DT Journal
FS 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Objective: To determine if GnRH-agonist (GnRH-a) could induce a LH surge in patients where a GnRH antagonist was used to prevent premature spontaneous LH surge. Design: Pilot study. Patients: Five patients treated with **ovarian** stimulation and IUI for idiopathic **infertility**. Main Outcome Measures: Luteinizing hormone, FSH, and P plasma levels. Results: A LH and FSH surge as

well as a P rise were obtained in the five patients studied. Conclusion: A GnRH-a successfully can induce an LH surge after GnRH antagonist **administration**. The effect of the antagonist on the quality of the GnRH-a- induced LH surge as well as the oocyte quality remain to be evaluated.

L46 ANSWER 8 OF 41 PROMT COPYRIGHT 1997 IAC

AN 96:404301 PROMT
TI Asta's **Cetrorelix** Enters Phase III Trials; NCE Update
SO Marketletter, (12 Aug 1996) pp. N/A.
ISSN: 0951-3175.
WC 245
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB Asta Medica has completed two dose-ranging clinical trials of its luteinizing hormone-releasing hormone antagonist **Cetrorelix** and is now starting its Phase III trials program in 800 women at multiple centers in Europe.
Two **administration** schedules have been selected for study in pivotal trials in women undergoing assisted **reproduction** techniques, one using multiple injections and one using a single injection, which have overcome the surge in LH which can compromise the controlled **ovarian** superovulation (COS) technique.
This is the first time that an LHRH antagonist has been tested in Phase II trials for COS.
Cetrorelix is also being assessed in other indications, and clinical Phase II trials are ongoing in patients with prostate cancer, benign prostatic hyperplasia and uterine myoma. It is in Phase I trials in Japan with partner Shionogi.
Meantime, Asta has reported that its novel antiepileptic drug D-23129 has completed Phase I testing in Germany, and that a first Phase II trial of a twice-daily oral regimen is scheduled to start this September. D-23129 was developed in cooperation with the US National Institutes of Health, and appears to modulate GABA via the opening of potassium channels.
Finally, Asta notes that it is now starting Phase I trials with two new anticancer agents, D-21266 and D-19575. D-21266 belongs to the same class as miltefosine for the topical treatment of metastases but can be given orally, while D-19575 is an alkylating agent with a glucose moiety which leads to more specific uptake by tumor cells.

L46 ANSWER 9 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 5
AN 95:501674 BIOSIS
DN 98525224
TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview.
AU Reissmann T; Felberbaum R; Diedrich K; Engel J; Comaru-Schally A M; Schally A V
CS ASTA Medica AG, Frankfurt/M., Germany
SO Human Reproduction (Oxford) 10 (8). 1995. 1974-1981. ISSN: 0268-1161
LA English
AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the **ovarian** cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the

number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After **administration** of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible new approaches to **ovarian** stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted **reproduction** technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for **ovarian** stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and **ovulation** induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

L46 ANSWER 10 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 6
AN 95:398004 BIOSIS
DN 98412304
TI Scheduled **administration** of a gonadotrophin-releasing hormone antagonist (**Cetrorelix**) on day 8 of in-vitro **fertilization** cycles: A pilot study.
AU Olivennes F; Fanchin R; Bouchard P; Taieb J; Selva J; Frydman R
CS Dep. Obstetrics Gynaecol. Lab. In Vitro Fertilization, Antoine Beclere Hosp., 157 Rue de la Porte de Trivaux, 92141 Clamart Cedex, France
SO Human Reproduction (Oxford) 10 (6). 1995. 1382-1386. ISSN: 0268-1161
LA English
AB To assess in a pilot study the ability of a single injection of a GnRH antagonist (**Cetrorelix**) to prevent premature luteinizing hormone (LH) surges in an in-vitro **fertilization** (IVF) embryo transfer programme when **administered** on a fixed day in the late follicular phase, **ovarian** stimulation was carried out in 11 women with two ampoules of human menopausal gonadotrophin per day beginning on day 2 of the menstrual cycle. A 3 mg dose of **Cetrorelix** was **administered** on day 8 of the stimulation cycle. A second injection was **administered** 72 h later if **ovulation** was not triggered in the meantime. We did not observe a premature LH surge in any of the cycles studied. The injection of 3 mg **Cetrorelix** was capable of preventing LH surge in all the patients studied, introducing a very simple treatment protocol. Among the patients who received two injections (n = 3), the day of the first **administration** was delayed in two subjects due to slow follicular maturation kinetics. Out of 11 patients, 10 had an embryo transfer. Four clinical pregnancies were obtained (40% per embryo transfer), of which 3 are ongoing (30% per embryo transfer). A simple **administration** protocol for a new GnRH antagonist (**Cetrorelix**) was able to prevent LH surges in the 11 patients studied.

L46 ANSWER 11 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 7
AN 95:303737 BIOSIS
DN 98318037
TI Evaluation of the in vitro and in vivo activity of the L-, D,L- and

D-Cit-6 forms of the LH-RH antagonist **Cetrorelix** (SB-75).

AU Pinski J; Schally A V; Yano T; Groot K; Srkalovic G; Serfozo P; Reissmann T; Bernd M; Deger W; Kutcher B; Engel J
CS VA Med. Cent., 1601 Perdido St., New Orleans, LA 70146, USA

SO International Journal of Peptide & Protein Research 45 (5). 1995. 410-417. ISSN: 0367-8377
LA English

AB The objective of this study was to examine the in vivo and in vitro gonadotropin-inhibiting potencies, edematogenic activities and the receptor binding affinities of the D-Cit-6, D,L-Cit-6 and L-Cit-6 forms of the LH-RH antagonist **Cetrorelix** (SB-75) (Ac-D-Nal(2)-1,D-Phe(4Cl)-2,D-Pal(3)-3,D-Cit-6,D-Ala-10)LH-RH. In order to demonstrate the suppressive effects of two different diastereomers of SB-75 and their racemic mixture on LH and FSH release, (D-Cit-6) SB-75 was injected subcutaneously in doses of 2.5 and 10 mu-g/rat, (D,L-Cit-6)-SB-75 in doses of 5 and 20 mu-g/rat and (L-Cit-6) SB-75 in doses of 12.5 and 50 mu-g/rat to castrated male rats. Two hours after **administration**, there was no difference in LH levels between rats injected with the L-form and control animals, indicating a low activity and/or a rapid enzymatic degradation of this peptide. The (1:1) diastereomeric mixture was only about half as potent in suppression of LH release compared to (D-Cit-6) SB-75. Serum FSH levels were suppressed significantly (p lt 0.01) for more than 48 h after the **administration** of 10 mu-g (D-Cit-6) SB-75 and 20 mu-g of (D,L-Cit-6) SB-75, respectively. (D-Cit-6) SB-75 **administered** at a dose of 2 mu-g/rat induced 100% inhibition of **ovulation**, while 4 mu-g/rat of the D,L-Cit-6 peptide were necessary to produce the same effect. (L-Cit-6) SB-75 given at a high dose of 40 mu-g/rat produced only 14% inhibition of **ovulation**. The D-Cit-6 form of SB-75 produced skin lesions with a much smaller diameter than the L-isomer, and was about 34 times less edematogenic. (D-Cit-6) SB-75 was bound more powerfully to high-affinity pituitary LH-RH receptors than either D,L-Cit-6 or L-Cit-6 analogues. In vitro assays based on the superfusion of dispersed rat pituitary cells on a column, followed by radioimmunoassay for LH, also demonstrated a lower inhibitory activity for the L-Cit-6 analogue, but the differences between D-, D,L- and L-citrulline analogues were smaller than in vivo. Our results indicate that the LH-RH antagonist (D-Cit-6) SB-75 is more effective in suppression of gonadotropin release in vivo and in vitro, less edematogenic and possesses higher binding affinity to pituitary LH-RH receptors than the D,L- and L-citrulline decapeptide analogues.

L46 ANSWER 12 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 95129571 EMBASE
TI **Cetrorelix**. D-20453 (as trifluoroacetate). D-20761 (as acetate). SB-75.
SO Drugs of the Future, (1995) 20/3 (299-300).
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal
FS 010 Obstetrics and Gynecology
016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LA English

L46 ANSWER 13 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 8
Searcher : Shears 308-4994

AN 95:128645 BIOSIS
DN 98142945
TI Inhibition of growth of human **ovarian** cancer in nude mice by luteinizing hormone-releasing hormone antagonist **Cetrorelix** (SB-75).
AU Manetta A; Gamboa-Vujicic G; Paredes P; Emma D; Liao S; Leong L; Asch B; Schally A
CS Div. Gynecol. Oncol., Univ. California, Irvine Med. Center, Build. 23, Route 81, 101 City Drive, Orange, CA 92613-1491, USA
SO Fertility and Sterility 63 (2). 1995. 282-287. ISSN: 0015-0282
LA English
AB Objective: To report on the in vitro and in vivo inhibitory effects of LH-releasing hormone (LH-RH) antagonist **Cetrorelix** (SB-75; Asta Medica, Frankfurt-Main, Germany) against a panel of human **ovarian** carcinomas. Interventions: In vitro studies: the effect of SB-75 was measured using a standardized chemosensitivity assay in the following **ovarian** cancer cell lines: UCI 101; UCI 107; PA-1; NIH: OVCAR 3; UCLA: 222; A2780, parental; A2780-CR, cisplatin resistant; A2780-DR, doxorubicin resistant; and the human breast cancer cell line, MCF-7. Results were expressed as percent growth inhibition determined by crystal violet photometric analysis. In vivo studies: the antiproliferative effect of this agent was examined using UCI-107, a primary epithelial **ovarian** carcinoma cell line, in a nude mouse model. On day 0, 10 times 10-6 UCI 107 cells were implanted subcutaneously into 20 intact female athymic nude mice (5 to 6 weeks old). On day 8, the mice were randomly divided into two groups of 10; control mice were implanted with miniosmotic pumps filled with a vehicle solution consisting of 5.2% mannitol in saline; and treated animals received pumps filled to deliver continuous **administration** of SB-75 at 60 jug per mouse per day. Results: In vitro studies: direct inhibition of cell proliferation by SB-75 was not observed at concentrations ranging from 1 nM to 100 mu-M (exposure lasting three to four cell doublings) with the exception of MCF-7, which demonstrated a 33% inhibition at the latter concentration. In vivo studies: on day 16, caliper measurements were taken from subcutaneous tumor nodules in SB-75treated and untreated mice and a significant difference of 270% in mean tumor volume was observed. End point was determined, on day 30, when control tumor volume approached 10,000 mm-3. At that time the difference in mean tumor volumes increased to 600%, indicating a substantial antiproliferative effect had been achieved in the SB-75-treated group. Conclusion: Our in vitro findings show direct inhibition by SB-75 on proliferation of human breast cancer cells. This direct inhibition in vitro was not observed in our **ovarian** cancer cell lines. However, in vivo SB-75 caused a significant inhibition of growth of human epithelial **ovarian** cancer. This may be a result of inhibition of the pituitary gonadal axis and gonadotropin secretion. Our results warrant further investigation.

L46 ANSWER 14 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 95221621 EMBASE
TI [The GnRH antagonists. Clinical prospects].
LES ANALOGUES ANTAGONISTES DE LA GNRH: PERSPECTIVES D'EMPLOI EN CLINIQUE.
AU Charbonnel B.; Dubourdieu S.
CS Clinique d'Endocrinologie, Maladies Metaboliques et Nutrition, Hotel-Dieu, BP 1005, 44035 Nantes Cedex 01, France
SO Revue Francaise d'Endocrinologie Clinique - Nutrition et Metabolisme, (1995) 36/3 (203-211).

ISSN: 0048-8062 CODEN: RECNAS
CY France
DT Journal
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LA French
SL English; French
AB GnRH antagonists suppress GnRH action by competitive inhibition with the endogenous GnRH. Their **administration** results in an immediate drop in LH and, to a lesser extent, FSH levels. The limits for their clinical consist in their histamine-releasing effect but the latter is reduced for the antagonists more recently available. Their use appears to be very promising in controlled **ovarian** hyperstimulation.

L46 ANSWER 15 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 9
AN 95:415178 BIOSIS
DN 98429478
TI Preserved pituitary response under **ovarian** stimulation with HMG and GnRH antagonists (**Cetrorelix**) in women with tubal **infertility**.
AU Felberbaum R E; Reissmann T; Kuepker W; Bauer O; Al Hasani S; Diedrich C; Diedrich K
CS Dep. of Obstetrics and Gynecology, Medical Univ. of Luebeck, Luebeck, Germany
SO European Journal of Obstetrics & Gynecology and Reproductive Biology 61 (2). 1995. 151-155. ISSN: 0301-2115
LA English
AB Objective: To examine the pituitary response in patients undergoing short-term application of the GnRH antagonist **Cetrorelix** in the mid-cycle phase for hypophysial suppression of premature LH surges within an IVF-program. Design: Twenty patients suffering from primary or secondary tubal **infertility** were stimulated with hMG from cycle day 2. From day 7 till **ovulation** induction **Cetrorelix** was **administered** in two different dose regimens (15 patients 3 mg s.c. daily; 5 patients 1 mg s.c. daily). Three hours before **ovulation** induction a GnRH test was performed using 25 mu-g of native GnRH and the pituitary response examined by measurement of the serum LH concentration after 30 min. Results: Premature LH surges could be avoided in the 3-mg group and in the 1-mg group, respectively. Due to this, none of the cycles had to be cancelled. Oestradiol profiles and ultrasound demonstrated a satisfactory follicular maturation. All patients showed pronounced suppression of the serum LH levels before **ovulation** induction. The mean increase of serum LH due to the performed GnRH test was 10 mIU/ml for the 3-mg group, while the average maximum in the 1-mg group was about 32.5 mIU/ml. Conclusions: The pituitary response is preserved by the treatment with the GnRH antagonist **Cetrorelix**. The extent of suppression of the adenohypophysis, as expressed by the different reactions on GnRH test, can be modulated by the dosage **administered**. This should allow **ovulation** induction by GnRH or one of its agonists instead of hCG, which could be beneficial in patients at high risk of **Ovarian** Hyperstimulation Syndrome (OHSS) and those suffering from Polycystic **Ovary** Disease (PCOD).

L46 ANSWER 16 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 10
AN 96:232794 BIOSIS
DN 98796923

TI GnRH-antagonists in **gynecology**: First results within controlled **ovarian** hyperstimulation (COH).
AU Felberbaum R; Reissmann T; Zoll C; Kuepker W; Al-Hasani S; Diedrich C; Diedrich K
CS Klinik Frauenheilkunde Geburtshilfe, Med. Univ. Luebeck, Ratzeburger Allee 160, D-23538 Luebeck, Germany
SO Gynaekologisch-Geburtshilfliche Rundschau 35 (SUPPL. 1). 1995. 113-117. ISSN: 1018-8843
LA German
AB Objective: Applicability of the GnRH-antagonist **Cetrorelix** within controlled **ovarian** hyperstimulation (COH) to avoid the premature LH-surge should be examined. Methods: 35 patients suffering from tubal **infertility** were stimulated for In Vitro **Fertilization** (IVF) by human menopausal gonadotrophins (HMG) and concomitant **administration** of **Cetrorelix** in different dosages (3 mg, 1 mg, 0.5 mg). Results: No premature LH-surge could be observed. Conclusions: Short term **administration** of the GnGR-antagonists avoids the occurrence of a premature LH-surge.

L46 ANSWER 17 OF 41 TOXLIT
AN 95:80648 TOXLIT
DN CA-123-047250E
TI Pharmacological influence on the **fertility** in man.
AU Neye H
CS Muenster
SO Dtsch. Apoth. Ztg, (1995). Vol. 135, No. 8, 39-40, pp. 42. CODEN: DAZEA. ISSN. 0011-9857.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA German
OS CA 123:47250
EM 9509
AB A review, with 7 refs., on the hormonal contraception in males by suppressing FSH, LH, and intratesticular testosterone and a simultaneous substitution of extratesticular testosterone. A combined **administration** of gonadorelin antagonist **cetrorelix** with 19-nortestosterone induces a complex a complete azospermia without side effects.

L46 ANSWER 18 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 11
AN 94:408132 BIOSIS
DN 97421132
TI Inhibition of growth of OV-1063 human epithelial **ovarian** cancer xenografts in nude mice by treatment with luteinizing hormone-releasing hormone antagonist SB-75.
AU Yano T; Pinski J; Halmos G; Szepeshazi K; Groot K; Schally A V
CS Endocrine, Polypeptide Cancer Inst., Veterans Affairs Med. Cent., New Orleans, LA 70146, USA
SO Proceedings of the National Academy of Sciences of the United States of America 91 (15). 1994. 7090-7094. ISSN: 0027-8424
LA English
AB Female athymic nude mice bearing xenografts of OV-1063 human epithelial **ovarian** cancer cell line were treated with potent luteinizing hormone (LH)-releasing hormone (LH-RH) antagonist SB-75 (**Cetrorelix**; (Ac-D-Nal(2)-1, D-Phe(4-Cl)-2, D-Pal(3)-3, D-Cit-6, D-Ala-10)LH-RH in which Ac-D-Nal(2) = N-acetyl-3-(2-naphthyl)-D-alanine, D-Phe(4Cl) = 4-chloro-D-phenylalanine, D-Pal(3) = 3-(3-pyridyl)-D-alanine, and D-Cit =

D-Citrulline) or with the agonist (D-Trp-6)LH-RH. In the first experiment, SB-75 and (D-Trp-6)LH-RH were **administered** in the form of microcapsules releasing 60 and 26 mu-g/day, respectively. In the second study, the analogs were given by daily s.c. injections in doses of 100 mu-g/day. In both experiments, tumor growth, as measured by reduction in tumor volume, percentage change in tumor volume, tumor burden, and increase in tumor doubling time, was significantly inhibited by treatment with SB-75 but not with (D-Trp-6)LH-RH. Uterine and **ovarian** weights were reduced and serum LH levels decreased by **administration** of either analog. Chronic treatment with SB-75 greatly reduced the concentration of receptors for epidermal growth factor and insulin-like growth factor I in tumor cell membranes, a phenomenon that might be related to tumor growth inhibition. It is possible that the antitumoral effects of SB-75 on OV-1063 **ovarian** cancers are exerted not only through the suppression of the pituitary-gonadal axis, but also directly. In view of its strong inhibitory effect on the growth of OV-1063 **ovarian** cancers in vivo, the potent LH-RH antagonist SB-75 might be considered for possible hormonal therapy of advanced epithelial **ovarian** carcinoma.

L46 ANSWER 19 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 12
AN 94:180571 BIOSIS
DN 97193571
TI Inhibitory effect of bombesin-gastrin-releasing peptide antagonist RC-3095 and luteinizing hormone-releasing hormone antagonist SB-75 on the growth of MCF-7 MIII human breast cancer xenografts in athymic nude mice.
AU Yano T; Pinski J; Szepeshazi K; Halmos G; Radulovic S; Groot K; Schally A V
CS Vet. Affairs Med. Cent., 1601 Perdido Street, New Orleans, LA 70146, USA
SO Cancer (Philadelphia) 73 (4). 1994. 1229-1238. ISSN: 0008-543X
LA English
AB Background. The results of several clinical trials using various luteinizing hormone-releasing hormone agonists for treatment of advanced breast cancer are encouraging. However, only about 30% of breast cancers are estrogen-dependent and can be treated by hormonal manipulation. New therapeutic approaches combining estrogen ablation therapy with other compounds must be explored. Various studies suggest that bombesin or gastrin-releasing peptide acts as an autocrine growth factor and may play a role in the initiation and progression of some cancers, including that of the breast. Methods. Female athymic nude mice bearing xenografts of the MCF-7 MIII human breast cancer cell line were treated for 7 weeks with bombesin/gastrin-releasing peptide antagonist (D-Tpi-6, Leu-13 psi(CH-2NH)-Leu-14) bombesin(6-14) (RC-3095) injected subcutaneously daily at a dose of 20 mu-g and luteinizing hormone-releasing hormone antagonist SB-75 (**Cetrorelix**) **administered** biweekly in the form of microgranules releasing 45 mu-g/day. Results. After 2 weeks of treatment, a significant inhibition of tumor volume was observed in the groups treated with RC-3095 alone or in combination with SB-75 but not in those treated with SB-75 as a single agent. After 7 weeks, tumor growth as measured by tumor volume and percentage changes in tumor volume and tumor weight was greatly inhibited in all of the treated groups. Uterine and **ovarian** weights were reduced and serum luteinizing hormone levels decreased by **administration** of SB-75 alone or in combination with RC-3095. Histologically, a significant decrease in argyrophilic nucleolar organizer region count in tumor cell nuclei was observed in

all of the treated groups, indicating a lower proliferation of these cells. High-affinity binding sites for bombesin were detected in cultured MCF-7 MIII cells. Chronic treatment with RC-3095 caused a significant down-regulation of epidermal growth factor receptors in tumor cell membranes, which might be related to tumor inhibition. In studies in vitro, SB-75 inhibited proliferation of MCF-7 cells in culture but not proliferation of MCF-7 MIII cells. Conclusions. Because previously we demonstrated that RC-3095 inhibits the proliferation of MCF-7 MIII cells in vitro, it appears that the major antitumoral effect of RC-3095 on the MCF-7 MIII cancer line is direct, whereas that of SB-75 is indirect, and that it is mediated by suppression of the pituitary-gonadal axis. In view of its immediate and powerful inhibitory effect on MCF-7 MIII tumors, bombesin/gastrin-releasing peptide antagonist RC-3095 might be considered as a possible new agent for the treatment of breast cancer.

L46 ANSWER 20 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 13
AN 95:128537 BIOSIS
DN 98142837
TI Treatment with luteinizing hormone-releasing hormone antagonist SB-75 decreases levels of epidermal growth factor receptor and its mRNA in OV-1063 human epithelial **ovarian** cancer xenografts in nude mice.
AU Shirahige Y; Cook C B; Pinski J; Halmos G; Nair R; Schally A V
CS Veterans Administration Med. Cent., 1601 Perdido St., New Orleans, LA 70146, USA
SO International Journal of Oncology 5 (5). 1994. 1031-1035. ISSN: 1019-6439
LA English
AB The aim of this study was to investigate the effect of **administration** of LH-RH antagonist SB-75 and agonist (D-Trp-6)LH-RH on receptors for epidermal growth factor (EGF) in OV-1063 human epithelial **ovarian** cancer. Female athymic nude mice bearing xenografts of OV-1063 human epithelial **ovarian** cancer were treated for 3 weeks with the modem LH-releasing hormone (LH-RH) antagonist (Ac-DNal(2)-1, D-Phe(4Cl)-2, D-Pal(3)-3, D-Cit-6, D-Ala-10) LH-RH (SB-75, **Cetrorelix**), the agonist (D-Trp-6)LH-RH, or bombesin/gastrin-releasing peptide antagonist RC-3095. SB-75 and (D-Trp-6) LH-RH were injected s.c. at doses of 100 mu-g/day, and RC-3095 was injected at a dose of 40 mu-g/day. Tumor growth, as measured by percentage change in tumor volume, was significantly inhibited by the treatment with SB-75, but not by (D-Trp-6) LH-RH or RC-3095. Treatment with SB-75 greatly decreased the levels of mRNA for EGF receptor and reduced the number of EGF binding sites on tumor membranes. Effects of SB-75 on EGF receptors might be related to inhibition of tumor growth. Our findings support the view that LH-RH antagonists such as SB-75 could be considered for possible hormonal therapy of epithelial **ovarian** cancer.

L46 ANSWER 21 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 14
AN 94:350777 BIOSIS
DN 97363777
TI Suppression of the endogenous luteinizing hormone surge by the gonadotropin-releasing hormone antagonist **Cetrorelix** during **ovarian** stimulation.
AU Diedrich K; Diedrich C; Santos E; Zoll C; Al-Hasani S; Reissmann T; Krebs D; Klingmueller D
CS Clinic Gynaecol. Obstetrics, Univ. Luebeck, Luebeck, GER

SO Human Reproduction (Oxford) 9 (5). 1994. 788-791. ISSN: 0268-1161
LA English
AB Surges of luteinizing hormone (LH) that result in luteinization but occur prematurely with respect to the diameter of the leading follicle, prevent attempts to induce multiple follicular maturation for in-vitro **fertilization** (IVF) in a significant number of women. We examined the possibility of blocking premature LH surges by the **administration** of **Cetrorelix**, a potent antagonist of gonadotrophin-releasing hormone (GnRH), in a study including 20 patients, some of whom had previously shown premature LH surges. All patients were treated with human menopausal gonadotrophins (HMG) starting on day 2. From day 7 until the induction of **ovulation** by human chorionic gonadotrophin (HCG) the GnRH antagonist **Cetrorelix** was given daily. HCG was injected when the dominant follicle had reached a diameter of gtoreq 18 mm and oestradiol concentration was gt 300 pg/ml for each follicle having a diameter of gt 15 mm. Oocyte collection was performed 36 h later by transvaginal ultrasound puncture, followed by IVF and embryo transfer. The hormone profiles of these patients and the results of IVF and embryo transfer are comparable to those treated with GnRH agonists and HMG. However, less time and especially less HMG is needed in comparison to patients stimulated with a long agonist protocol. Hence, treatment with **Cetrorelix** proved to be much more comfortable for the patient. In this study we showed that combined treatment with gonadotrophins and the GnRH antagonist **Cetrorelix** is a promising method for **ovarian** stimulation in patients who frequently exhibit premature LH surges and therefore fail to complete treatment.

L46 ANSWER 22 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 94179320 EMBASE
TI Introduction of LHRH-antagonists into the treatment of gynaecological disorders.
AU Reissmann Th.; Diedrich K.; Comaru-Schally A.M.; Schally A.V.
CS Clinic Obstetrics and Gynaecology, University of Lubeck, Lubeck, Germany, Federal Republic of
SO HUM. REPROD., (1994) 9/5 (767-769).
ISSN: 0268-1161 CODEN: HUREEE
CY United Kingdom
DT Journal
FS 010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
030 Pharmacology
037 Drug Literature Index
LA English

L46 ANSWER 23 OF 41 MEDLINE
AN 95119265 MEDLINE
TI Differential regulation of gonadotropin synthesis and release in **ovariectomized** ewes after treatment with a luteinizing hormone-releasing hormone antagonist.
AU Sanchez T; Wehrman M E; Moss G E; Kojima F N; Cupp A S; Bergfeld E G; Peters K E; Mariscal V; Grotjan H E Jr; Kinder J E; et al
CS Department of Animal Science, University of Nebraska, Lincoln 68583-0908.
SO BIOLOGY OF REPRODUCTION, (1994 Oct) 51 (4) 755-9.
Journal code: A3W. ISSN: 0006-3363.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 9504
AB Our working hypothesis was that synthesis and release of LH, but not FSH, were solely dependent on LHRH. Twenty **ovariectomized** (OVX) ewes were randomly assigned to one of five treatments (n = 4 per group). Ewes were **administered** a low (10 micrograms/kg) or high (100 micrograms/kg) dose of LHRH antagonist (LHRH-Ant) at 24-h intervals for 3 or 6 days. Control ewes received vehicle (5% mannitol) at 24-h intervals for 6 days. Blood samples were collected every 15 min for 4 h before LHRH-Ant or vehicle and every 2 h during the period of treatment to determine concentrations of LH and FSH. Twenty-four hours after the last treatment with LHRH-Ant or vehicle, anterior pituitaries were collected and divided in half along the midsagittal plane; the number of receptors for LHRH, pituitary content of LH and FSH, and relative amounts of mRNA for alpha, LH beta, and FSH beta subunits were determined. Concentrations of LH in serum decreased ($p < 0.05$) from 25.4 +/- 4.3 ng/ml before LHRH-Ant to less than 0.5 ng/ml within 4 h after the first treatment of LHRH-Ant and remained low (< 0.5 ng/ml) throughout the study. Serum concentrations of FSH declined gradually during the 3- or 6-day period of treatment with LHRH-Ant, from 37.3 +/- 2.4 and 26.5 +/- 4.8 ng/ml to 19.9 +/- 1.8 and 13.7 +/- 2.1 ng/ml, respectively. The magnitude of decline in serum concentrations of LH and FSH did not differ among ewes treated with low or high doses of LHRH-Ant.(ABSTRACT TRUNCATED AT 250 WORDS)

L46 ANSWER 24 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 15
AN 94:454786 BIOSIS
DN 97467786
TI The single or dual **administration** of the gonadotropin-releasing hormone antagonist **cetrorelix** in an in vitro **fertilization**-embryo transfer program.
AU Olivennes F; Taieb J; Fanchin R; Selva J; Bouchard P; Frydman R; De Ziegler D
CS Dep. Obstetrics Gynecol., Antoine Beclere Hosp., 157 rue de la Porte de Trivaux, 92141 Clamart Cedex, FRA
SO Fertility and Sterility 62 (3). 1994. 468-476. ISSN: 0015-0282
LA English
AB Objective: To assess the ability of a GnRH antagonist (**Cetrorelix**, Asta Medica AG, Frankfurt, Germany) to prevent premature LH surges in an IVF-ET program using a simple protocol with one or two **administrations**. Design: Controlled **ovarian** hyperstimulation was carried out in 17 women with three ampules a day of hMG, starting on day 2 of the menstrual cycle. A dose of 5 mg of **Cetrorelix** was **administered** when plasma E-2 levels were between 150 and 200 pg/mL (conversion factor to S1 unit, 3.671) per follicle of gtoreq 14 mm. A second injection was performed 48 hours later if the triggering of **ovulation** was not decided in the meantime. Results: Six patients received one injection and 11 patients received two **administrations**. Plasma LH levels showed a marked decrease and remained low after the **administration** of the GnRH antagonist. In six patients, the first **administration** of **Cetrorelix** was performed when a significant rise in LH plasma level was present. Even in these patients the GnRH antagonist was able to prevent an LH surge. The tolerance of the product was good. Six clinical pregnancies were obtained, of which four are ongoing (25% per ET). Two ongoing pregnancies were obtained after the transfer of a frozen-thawed embryo (35.3% per retrieval). Conclusions: The GnRH antagonist **Cetrorelix** in a simple,

unique or dual **administration**, protocol was able to prevent premature LH surge in all of the 17 patients studied. If these results are confirmed by larger, randomized studies, the good tolerance and efficacy that we observed suggest a bright future for this product in assisted **reproductive** technologies.

L46 ANSWER 25 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 16
AN 94:454785 BIOSIS
DN 97467785
TI A single injection of a gonadotropin-releasing hormone (GnRH) antagonist (**Cetrorelix**) postpones the luteinizing hormone (LH) surge: Further evidence for the role of GnRH during the LH surge.
AU Leroy I; Frydman R; Diacremont M F; De Mouzon J; Brailly-Tabard S; Bouchard P
CS Service Endocrinol., Hopital Saint Antoine, rue du Fg Saint Antoine, 75012 Paris, FRA
SO Fertility and Sterility 62 (3). 1994. 461-467. ISSN: 0015-0282
LA English
AB Objectives: To assess the ability of a new third-generation GnRH antagonist, **Cetrorelix** (Asta Medica AG, Frankfurt am Main, Germany), to postpone the LH surge after a single injection during the late follicular phase. Design: A single 5-mg (group 1, n = 7) or 3-mg (group 2, n = 3) dose SC of **Cetrorelix** was **administered** during the late follicular phase, on the day of the cycle when plasma E-2 exceeded 150 pg/mL (550 pmol/L). Estradiol, LH, FSH, and P levels were measured daily from day 5 of the cycle until day 10 after antagonist **administration**. Transvaginal ultrasonographies were performed on the day of injection and after antagonist treatment. Subjects: Ten normal women with regular **ovulatory** menstrual cycles. Results: In group 1, **Cetrorelix** was **administered** on day 14.6 +- 5 (mean +- SD) of the cycle, when the mean plasma E2 level was 181 +- 32 pg/mL (664 +- 117 pmol/L) (mean +- SD). Plasma LH and FSH decreased by 56% +- 19% and 29.5% +- 16% (mean +- SD), respectively, reaching the nadir 24 hours after **Cetrorelix administration**. Estradiol decreased by 85% +- 17%, reaching the nadir 48 hours after antagonist injection. In group 2, **Cetrorelix** was **administered** on day 14.3 +- 1.2 of the cycle when the mean plasma E-2 level was 169 +- 21 pg/mL (618 +- 77 pmol/L). Plasma LH and FSH decreased by 66% +- 18% and 32% +- 6%, respectively, reaching a nadir 24 hours after **Cetrorelix administration**. Estradiol decreased by 81% +- 9%, reaching the nadir 24 to 48 hours after antagonist **administration**. The LH surge was interrupted in every case. In six of seven subjects from group 1, the LH surge was delayed, occurring 6 to 17 days after the antagonist injection. In the remaining woman, **Cetrorelix** was **administered** at the beginning of the LH surge (LH = 13 IU/L): the LH level fell immediately by 54%, and the surge was postponed by 3 days. In group 2, in three of three subjects, the LH surge was delayed, occurring 6 to 9 days after the antagonist injection. No adverse effects were observed, except for very slight and transient erythema and pruritis at the injection site. Conclusion: **Cetrorelix** is a very potent new GnRH antagonist. A single injection during the late follicular phase delays the LH surge, even if the latter has already begun. In addition, this new-generation GnRH antagonist is very well tolerated and simple to use. Our data reinforce the role of GnRH during the LH surge and point to a role for new GnRH antagonists in controlled **ovarian** hyperstimulation to avoid premature LH surges and subsequent

luteinization.

L46 ANSWER 26 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 17
AN 94:504647 BIOSIS
DN 97517647
TI Seven-day **administration** of the gonadotropin-releasing hormone antagonist **cetrorelix** in normal cycling women.
AU Sommer L; Zanger K; Dyong T; Dorn C; Luckhaus J; Diedrich K; Klingmueller D
CS Institut fuer Klinische Biochemie der Universitaet Bonn, Sigmund Freud Str. 25, D-53105 Bonn, GER
SO European Journal of Endocrinology 131 (3). 1994. 280-285.
LA English
AB In contrast to gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists do not show any stimulatory effect on the pituitary but their clinical usage was precluded by severe side effects and high dose requirements. We report here on a 7-day treatment using the potent GnRH antagonist **Cetrorelix** ((Ac-D-Nal(2)-1, D-Phe(4Cl)-2, D-Pal(3)-3, D-Cit-6, D-Ala-10)GnRH) on five women 23-33 years old. All women were **ovulatory** and were studied during three consecutive cycles: a control cycle, a treatment cycle and a posttreatment control cycle. Throughout the control cycles blood samples were obtained daily during cycle days 8-18 and on days 21 and 23 during the remainder of the control cycles. On the eighth day of the treatment cycle women were hospitalized at 07.00 h for 2 6 h. Repeated blood samples were drawn at 15-min intervals during the entire period. Subjects received 3 mg of **Cetrorelix** sc for the first time at 09.00 h on the eighth day of the cycle and dally at 08.00 h for the following 6 days. Blood samples were obtained daily over a period of 25 days and every third day throughout the remainder of the treatment cycle. Twenty-four hours after the first application of **Cetrorelix**, luteinizing hormone (LH) and estradiol were in the subnormal range and remained subnormal until the end of medication. The suppressive effect of **Cetrorelix** compared to pretreatment values lasted at least 6 days for LH and FSH and 11 days after the last **Cetrorelix** injection for estradiol. An LH surge followed by postovulatory progesterone values was found 22.6 +- 1.4 days after the last injection. During application of the GnRH antagonist, LH was reduced to 16.1 +- 0.7%, FSH to 58.7 +- 1.3% and estradiol to 17.9 +- 0.4% compared to the individual pretreatment values. The consecutive cycle after completion of treatment was comparable to the length of the pretreatment cycle. No serious side effects were observed. In summary, the results of this study give evidence of the effectiveness and safety of this new GnRH antagonist used in low dosages for possible therapeutic application in sex-hormone-dependent diseases in women.

L46 ANSWER 27 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 18
AN 94:363779 BIOSIS
DN 97376779
TI Suppression of the endogenous LH increase in **ovarian** stimulation by GnRH antagonist **cetrorelix**.
AU Diedrich K; Diedrich C; Santos E; Bauer O; Zoll C; Al-Hasani S; Reissmann T; Krebs D; Klingmueller D
CS Klinik Frauenheilkunde Geburtshilfe, Med. Univ. Luebeck, Ratzeburger Allee 160, 23562 Luebeck, GER
SO Geburtshilfe und Frauenheilkunde 54 (4). 1994. 237-240. ISSN: 0016-5751
LA German
AB Surges of LH in serum, which result in luteinisation, but occur

prematurely with respect to the diameter of the leading follicle, frustrate attempts to induce multiple follicular maturation for in-vitro **fertilisation** in a number of women. We examined the possibility of blocking premature LH-surges by the **administration** of **Cetrorelix**, a potent antagonist of gonadotrophin releasing hormone. Twenty patients, who had repeatedly shown premature LH surges, were treated with human menopausal gonadotrophins from the 2nd day onwards. From the 7th day until the induction of **ovulation** by HCG, the GNRH-antagonist **Cetrorelix** was given daily. HCG was injected when the dominant follicle had reached the diameter of at least 18 mm and oestradiol levels were above 300 pg for each follicle and more than 15 mm. Oocyte collection was performed 36 hours later by transvaginal ultrasound puncture, followed by IVF and embryo transfer. The hormone profiles of these patients and the results of in-vitro **fertilisation** and embryo transfer are discussed. It could be demonstrated in this study, that combined treatment with gonadotrophins and the GNRH-antagonist seems to be a promising method for **ovarian** stimulation in patients, who frequently exhibit premature LH discharges and therefore fail to complete treatment.

L46 ANSWER 28 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 94130907 EMBASE
TI FDA recommendations for preclinical testing of gonadotropin releasing hormone (GnRH) analogues.
AU Raheja K.L.; Jordan A.
CS Div. Metabolism/Endocrine Drug Prod., US Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, United States
SO REGUL. TOXICOL. PHARMACOL., (1994) 19/2 (168-175).
ISSN: 0273-2300 CODEN: RTOPDW
CY United States
DT Journal
FS 016 Cancer
022 Human Genetics
030 Pharmacology
052 Toxicology
037 Drug Literature Index
LA English
SL English
AB Gonadotropin-releasing hormone (GnRH) agonists and antagonists are synthetic analogues synthesized by modifications of the naturally occurring hypothalamic decapeptide GnRH. These modifications significantly increase the biological potency and duration of action of GnRH agonists as well as the solubility, potency, and duration of action of GnRH antagonists while decreasing GnRH antagonists toxicity. The field of GnRH analogues has expanded significantly during the past few years in terms of the number of analogues, therapeutic indications, formulations, and mode of **administration**. This paper provides recommendations for nonclinical testing of GnRH analogues and reflects the type and degree of toxicity testing expected by the Division. However, these recommendations are not formal guidelines in that alternative testing methods will be considered. Furthermore, these recommendations should not be used as guidance for testing of other new drugs.

L46 ANSWER 29 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 94113671 EMBASE
TI The effect of androgens and antiandrogens on the immunohistochemical

localization of the androgen receptor in accessory **reproductive** organs of male rats.

AU Paris F.; Weinbauer G.F.; Blum V.; Nieschlag E.

CS Institute of Reproductive Medicine, University of Munster, Steinfurter Strasse 107, 48149 Munster, Germany, Federal Republic of

SO J. STEROID BIOCHEM. MOL. BIOL., (1994) 48/1 (129-137).
ISSN: 0960-0760 CODEN: JSBBEZ

CY United Kingdom

DT Journal

FS 003 Endocrinology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB The androgen receptor (AR) was localized immunohistochemically after different hormonal treatments in the ventral prostate, coagulating gland, seminal vesicle and epididymis of the adult rat. In the untreated controls AR-immunoreactivity was confined to the cell nuclei. One week after castration or treatment with the gonadotropin-releasing hormone antagonist **Cetrorelix** (150 .mu.g/animal per day) a cytoplasmic staining occurred in the epithelial cells of the ventral prostate and in part of the coagulating gland and seminal vesicle. In contrast, the AR remained exclusively in the nuclei in the epididymal epithelium and the glandular smooth muscle layer even after 2 weeks of androgen depletion. Bolus injections of either dihydrotestosterone (1 mg/kg), the antiandrogen flutamide (40 mg/kg), or the novel non-steroidal antiandrogen casodex (40 mg/kg) to androgen-depleted animals eliminated cytoplasmic AR-immunoreactivity and restored the nuclear staining pattern in the ventral prostate. A sustained 2-week treatment with the antiandrogens resulted in a loss of weight in all organs but did not alter the distribution of AR-immunoreactivity. The data show an apparent cytoplasmic/nuclear ligand-dependent translocation of the AR in the ventral prostate, coagulating gland and seminal vesicle but not in the epididymis of the adult rat.

L46 ANSWER 30 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.

AN 94152371 EMBASE

TI Control of the preovulatory luteinizing hormone surge by gonadotropin- releasing hormone antagonists: Prospects for clinical application.

AU Fraser H.M.; Bouchard P.

CS MRC Reproductive Biology Unit, Edinburgh EH9 3EW, United Kingdom

SO TRENDS ENDOCRINOL. METAB., (1994) 5/2 (87-93).
ISSN: 1043-2760 CODEN: TENME4

CY United States

DT Journal

FS 003 Endocrinology
010 Obstetrics and Gynecology
037 Drug Literature Index

LA English

SL English

AB The preovulatory LH surge of the primate menstrual cycle represents a number of positive influences, a major component of which is a direct action of estradiol on the anterior pituitary lobe. Whether the LH surge also requires a corresponding burst of GnRH release from the hypothalamus has been debated. After many years of investigation, there is now conclusive evidence that a midcycle GnRH surge does occur in the primate. This is supported by studies in

women with normal **ovulatory** cycles that demonstrate that blockade of the GnRH receptor by potent GnRH antagonists **administered** within 1-2 days of the expected midcycle can delay the LH surge. The ability to prevent the positive feedback effects of estradiol by GnRH antagonists is being employed for the controlled induction of follicular development and **ovulation** in the treatment of **infertility** and in in vitro **fertilization** programs.

L46 ANSWER 31 OF 41 PROMT COPYRIGHT 1997 IAC

AN 94:429325 PROMT
TI Yano, T.; Pinski, J.; Halmos, G.; Szepeshazi, K.; Groot, K.; Schally, A.V. Hormonal Therapy Epithelial **Ovarian** Carcinoma. Inhibition of Growth of OV-1063 Huma
SO Cancer Researcher Weekly, (5 Sep 1994) pp. N/A.
WC 345
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB SOURCE: Proceedings of the National Academy of Sciences of the United States of America, July 19, 1994;91(15):7090-7094.
According to the authors' abstract of an article published in Proceedings of the National Academy of Sciences of the United States of America, "Female athymic nude mice bearing xenografts of OV-1063 human epithelial **ovarian** cancer cell line were treated with potent luteinizing hormone (LH)-releasing hormone (LH-RH) antagonist SB-75 (**Cetrorelix**; (Ac-D-Nal(2)(1), D-Phe(4 Cl)(2), D-Pal(3)(3), D-Cit(6), D-Ala(10))LH-RH in which Ac-D-Nal(2) = N -acetyl-3-(2-naphthyl)-D-alanine, D -Phe(4Cl) = 4-chloro-D-phenylalanine, D -Pal(3) = 3-(3 -pyridyl)-D-alanine, and D-Cit = D-Citrulline) of with the agonist (D-Trp(6))LH-RH. In the first experiment, SB-75 and (D-Trp(6))LH-RH were **administered** in the form of microcapsules releasing 60 and 25 ug/day, respectively. In the second study, the analogs were given by daily s.c. injections in doses of 100 ug/day. In both experiments, tumor growth, as measured by reduction in tumor volume, percentage change in tumor volume, tumor burden, and increase in tumor doubling time, was significantly inhibited by treatment with SB-75 but not with (D-Trp(6))LH-RH. Uterine and **ovarian** weights were reduced and serum LH levels decreased by **administration** of either analog. Chronic treatment with SB-75 greatly reduced the concentration of receptors for epidermal growth factor and insulin-like growth factor I in tumor cell membranes, a phenomenon that might be related to tumor growth inhibition. It is possible that the antitumoral effects of SB-75 on OV-1063 **ovarian** cancers are exerted not only through the suppression of the pituitary-gonadal axis, but also directly. In view of its strong inhibitory effect on the growth of OV-1063 **ovarian** cancers in vivo, the potent LH-RH antagonist SB -75 might be considered for possible hormonal therapy of advanced epithelial **ovarian** carcinoma." The corresponding author for this study is: T Yano, Vet ADM Med Ctr, Inst Endocrine Polypeptide & Canc, New Orleans, LA 70146 USA. For subscription information for this journal contact the publisher: Natl Acad Sciences, 2101 Constitution Ave NW, Washington, DC 20418.

L46 ANSWER 32 OF 41 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 19
AN 94:395735 BIOSIS
DN 97408735
TI Recovery of Pituitary-Gonadal Function in Male Rats after Long-Term

Suppression Induced by a Single Injection of Microcapsules of LH-RH Antagonist **Cetrorelix** (SB-75).

AU Pinski J; Yano T; Szepeshazi K; Groot K; Schally A V

CS VA Med. Cent., 1601 Perdido St., New Orleans, LA 70146, USA

SO Journal of Andrology 14 (3). 1993. 164-169. ISSN: 0196-3635

LA English

AB The clinical utility of luteinizing hormone-releasing hormone (LH-RH) analogs can be greatly enhanced by a sustained delivery system, which could maintain elevated peptide levels in the blood for prolonged periods of time, up to several weeks. Recently, we developed long-acting microcapsules and microgranules of the LH-RH antagonist SB-75. In this study, we examined the suppressive effects of a single injection of microcapsules of antagonist SB-75 on gonadotropin and testosterone secretion, as well as on **fertility**, in male rats and the reversibility of those effects. Serum SB-75 levels were measured by RIA. A dose of 20 mg of microcapsules/rat containing 3.58 mg of antagonist in poly(D,L-lactide-co-glycolide), **administered** intramuscularly produced SB-75 levels higher than 20 ng/ml for approximately 24 days, and a significant elevation was maintained until day 90. Serum testosterone was decreased to castration values for 164 days and LH levels were suppressed below the detection limit of the RIA for a period of 102 days. Serum FSH was suppressed by more than 90%, as compared to control animals, for a period of 58 days and remained significantly decreased until day 164 after the injection. This treatment also caused a significant decrease in the weights of the testes, seminal vesicles, and ventral prostate 30 days after peptide **administration**. The histology of the testes from the treated rats showed that spermatogenesis was totally depressed. No mature elongated or round spermatids were found in the seminiferous tubules, spermatocytes being the most advanced germ cell form in 99.5% of the testicular tubules. Ten months after injection, a complete recovery in organ weights, hormonal levels, and **fertility** was observed. Histological studies revealed a complete recovery of spermatogenesis, with 100% of seminiferous tubules containing mature elongated spermatids. All treated rats proved to be able to impregnate normal female rats. The offspring were normal, with no evidence of genetic abnormalities. The overall results demonstrate the efficacy of SB-75 microcapsules in suppressing the pituitary-gonadal axis for a prolonged period of time and show that the long-term suppression of gonadal function induced by chronic treatment with antagonist SB-75 is completely reversible.

L46 ANSWER 33 OF 41 MEDLINE DUPLICATE 20

AN 94088825 MEDLINE

TI Inhibitory effect of a highly potent antagonist of LH releasing hormone (SB-75) on the pituitary gonadal axis in the intact and castrated rat.

AU Ayalon D; Farhi Y; Comaru-Schally A M; Schally A V; Eckstein N; Vagman I; Limor R

CS Timsit Institute of Reproductive Endocrinology, Sourasky Medical Center of Tel Aviv, Israel..

SO NEUROENDOCRINOLOGY, (1993 Aug) 58 (2) 153-9.
Journal code: NY8. ISSN: 0028-3835.

CY Switzerland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9403

AB The biological potency of the new, highly potent antagonist

[AC-D-Nal (2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10] LH-RH (SB-75) on the pituitary-gonadal system of female castrated and intact **ovulating** rats was tested. **Administration** of a single dose (50-100 micrograms/kg BW) of the antagonist SB-75 inhibited effectively the elevated gonadotrophin levels for 48 h. Pituitary LH and FSH content was not affected by SB-75 treatment. When **administered** in the early afternoon of the proestrus to intact cycling rats, SB-75 blocked the preovulatory LH surge as well as the primary and secondary FSH surges. However, the secondary FSH surge was not affected by SB-75 treatment when **administered** on the evening of proestrus suggesting its independence from the LH-RH mechanism. A group of **ovariectomized** rats was chronically treated with D-Trp6-LH-RH after having been pretreated by **administration** of a single dose of the antagonist. The initial stimulatory release of LH and FSH initiated by injection of the LH-RH agonist was significantly reduced by pretreatment with the LH-RH antagonist. We conclude that the LH-RH antagonist SB-75 may be used effectively in the field of **reproductive** dysfunction and endocrinological oncology and may become an invaluable physiological probe in studying the hormonal dynamics of the **reproductive** endocrine axis.

L46 ANSWER 34 OF 41 MEDLINE DUPLICATE 21
AN 93126305 MEDLINE
TI Somatostatin analogue RC-160 and LH-RH antagonist SB-75 inhibit growth of MIA PaCa-2 human pancreatic cancer xenografts in nude mice.
AU Radulovic S; Comaru-Schally A M; Milovanovic S; Schally A V
CS Endocrine, Polypeptide, and Cancer Institute, Veterans Affairs Medical Center, New Orleans, Louisiana 70146..
NC CA 40077 (NCI)
SO PANCREAS, (1993 Jan) 8 (1) 88-97.
Journal code: PRS. ISSN: 0885-3177.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9304
AB Nude mice bearing xenografts of the MIA PaCa-2 human pancreatic cancer cell line were treated with sustained-release formulations (microcapsules) of luteinizing hormone releasing hormone (LH-RH) agonist [D-Trp6]-LH-RH, somatostatin analogue RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2), or combination of both analogues. Other groups of mice received daily subcutaneous injections of LH-RH antagonist SB-75 [Ac-D-Nal(2)',D-Phe(4Cl)2,D-Pal(3)3,D-Cit6,D-Ala10-LH-RH] or bombesin antagonist RC-3095. At necropsy, in mice given microcapsules releasing 25 micrograms/day of [D-Trp6]-LH-RH, tumor weight and volume were decreased, but not significantly, as compared with control mice. Microcapsules of RC-160, releasing 25 micrograms/day, significantly reduced tumor volume, percentage change in tumor volume, and tumor weight. Combination of RC-160 and [D-Trp6]-LH-RH inhibited tumor growth to a somewhat greater extent than RC-160 alone. Bombesin antagonist RC-3095, at a dose of 25 micrograms/day, did not influence the growth of tumors. In mice receiving 100 micrograms/day of antagonist SB-75, there was a significant decrease in tumor weight and volume and a significant reduction in the weight of **ovaries** and uteri. Specific binding of [125I]RC-160 and [125I][D-Trp6]-LH-RH, but not [125I]Tyr4-bombesin, was found on MIA

PaCa-2 cells in culture. [D-Trp6]-LH-RH, SB-75, and RC-160 inhibited the growth of MIA PaCa-2 cells in vitro. Neither bombesin nor RC-3095 influenced the growth of MIA PaCa-2 cells in cultures. The results indicate that the LH-RH antagonist SB-75 could be tried for treatment of pancreatic cancer. Our findings confirm the efficacy of somatostatin analogue RC-160 in inhibiting the growth of pancreatic cancers and suggest that the combination of RC-160 and agonist [D-Trp6]-LH-RH might possibly increase the therapeutic response.

L46 ANSWER 35 OF 41 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 93042830 EMBASE
TI [GnRH antagonists].
LES ANTAGONISTES DE LA GNRH.
AU Charbonnel B.; Bouchard P.
CS Clinique d'Endocrinologie, Maladies Metaboliques, Nutrition, Hotel-Dieu, F 44000 Nantes, France
SO GYNECOLOGIE, (1992) 43/6 (339-343).
ISSN: 0301-2204 CODEN: GYNCAZ
CY France
DT Journal
FS 003 Endocrinology
010 Obstetrics and Gynecology
037 Drug Literature Index
LA French

L46 ANSWER 36 OF 41 MEDLINE DUPLICATE 22
AN 92385842 MEDLINE
TI Growth inhibition of estrogen independent MXT mouse mammary carcinomas in mice treated with an agonist or antagonist of LH-RH, an analog of somatostatin, or a combination.
AU Szepeshazi K; Milovanovic S; Lapis K; Groot K; Schally A V
CS Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA 70146..
NC CA40004 (NCI)
SO BREAST CANCER RESEARCH AND TREATMENT, (1992) 21 (3) 181-92.
Journal code: A8X. ISSN: 0167-6806.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9212
AB Female BDF1 mice inoculated with MXT (3.2) estrogen independent mouse mammary carcinoma were treated for three weeks with microcapsules of the luteinizing hormone-releasing hormone (LH-RH) agonist [D-Trp6]LH-RH, the antagonist SB-75, the somatostatin analog RC-160, or combinations. The lack of estrogen dependence of the tumor was proved by bilateral surgical **ovariectomy**, which had no effect. In two experiments, treatment with 25 micrograms/day doses of each analog alone resulted in a significant inhibition of tumor growth as shown by a 40-53% inhibition of tumor volumes, 38-43% decrease in tumor weights, and histological signs of tumor regression. However, the combination of SB-75 or [D-Trp6]LH-RH with somatostatin analog RC-160 caused greater reduction of tumor volume (68 and 61%) or tumor weights (59 and 56%), than single analogs, and histologically the occurrence of apoptosis and decrease in AgNOR numbers was more pronounced in the groups receiving combination therapy. Specific binding sites for [D-Trp6]LH-RH, EGF, and IGF-I were demonstrated in the tumor membranes. The binding capacity of LH-RH receptors was decreased by treatment with the analogs, the greatest down-regulation being caused by combination therapy. A

significant decrease in EGF binding capacity was observed after treatment with the LH-RH analogs, alone or especially in combination with somatostatin analog RC-160. The combination of these analogs also caused a reduction in IGF-I receptors. The finding that LH-RH agonists and antagonists and somatostatin analogs inhibit the growth of estrogen independent mammary tumors, and that combinations are more effective than single analogs, might be of practical importance in human breast cancer therapy.

L46 ANSWER 37 OF 41 MEDLINE DUPLICATE 23
AN 92105175 MEDLINE
TI Treatment of experimental DMBA induced mammary carcinoma with **Cetrorelix** (SB-75): a potent antagonist of luteinizing hormone-releasing hormone.
AU Reissmann T; Hilgard P; Harleman J H; Engel J; Comaru-Schally A M; Schally A V
CS ASTA Pharma AG, Frankfurt, Federal Republic of Germany..
SO JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1992) 118 (1) 44-9.
Journal code: HL5. ISSN: 0171-5216.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9204
AB **Cetrorelix**, (Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10)-LHRH (SB-75) is a new highly potent antagonist of LH-RH. In the model of DMBA-induced mammary carcinoma, this antagonist was very effective in reducing tumor mass. A rapid decrease in tumor weights to levels below 0.1 g total tumor mass was achieved with 300 micrograms/kg given sc. daily for 14 days. The weights of uteri and **ovaries** were reduced to about 40-50% of control values. In all treated rats the estrus cycle was interrupted and the animals remained in a state of anestrus. Microscopically, the effects of **Cetrorelix** on the tumors were characterized by a loss of mitotic activity, marked regression with apoptosis, an increase of stroma and differentiation towards a normal mammary architecture. On the basis of a dose-response curve, a dose of 100 micrograms/kg/d of **Cetrorelix** was determined as sufficient for a full antitumor response. Large DMBA-tumors with total tumor mass of about 6 g could also be treated very effectively with a dose of 100 micrograms/kg/d. To achieve a complete tumor regression, the treatment had to last 34 days. After the cessation of treatment with 100 micrograms/kg/d and regrowth of the tumors the animals were treated with the agonist Decapeptyl (Trp6-LHRH) using a dose of 50 micrograms/rat/d for 14 days. Again, the tumors responded well and regressed within 10 days. The treatment with an overlapping dose schedule of **Cetrorelix** and Decapeptyl showed a continuous antitumor response. A transient stimulation of tumor growth by the LH-RH agonist was not observed under these experimental conditions. In **ovariectomized** rats bearing DMBA-tumors, treatment with **Cetrorelix** and estradiol, produced no tumor growth inhibition as compared to estradiol control group, indicating that there is no estrogen nullifying effect of this antagonist on tumor cells in this model. On the basis of these results, **Cetrorelix** is a highly effective antitumor agent in this breast cancer model, which might also be useful under clinical conditions.

L46 ANSWER 38 OF 41 MEDLINE

AN 93004795 MEDLINE
TI Inhibition of growth of MCF-7 MIII human breast carcinoma in nude mice by treatment with agonists or antagonists of LH-RH.
AU Yano T; Korkut E; Pinski J; Szepeshazi K; Milovanovic S; Groot K; Clarke R; Comaru-Schally A M; Schally A V
CS Endocrine, Polypeptide and Cancer Institute, Veterans Administration Medical Center, New Orleans, LA 70146.
NC CA 40004 (NCI)
SO BREAST CANCER RESEARCH AND TREATMENT, (1992) 21 (1) 35-45.
Journal code: A8X. ISSN: 0167-6806.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9301
AB Human breast carcinoma (MCF-7 MIII), which exhibits an estrogen-independent but estrogen-responsive phenotype, was xenografted in 8-9-week-old intact female athymic nude mice without estrogen supplementation. In this model, we investigated inhibitory effects of the modern luteinizing hormone-releasing hormone (LH-RH) antagonist SB-75 and the agonist D-Trp6-LH-RH. The analogs were **administered** in the form of sustained delivery systems (microcapsules and microgranules). In the first experiment, treatment lasted 10 weeks. After 9 weeks of treatment, a significant inhibition of tumor volume was first found only in the group treated with SB-75, but the final tumor volume was significantly suppressed both by D-Trp6-LH-RH and SB-75. In the second experiment, treatment was started 70 days after tumor transplantation and was continued for 6 weeks. Chronic treatment with SB-75 or D-Trp6-LH-RH appeared to completely arrest tumor growth as measured by tumor volume, percentage change in tumor volume, and tumor weight. Serum estradiol was suppressed to undetectable levels and LH levels were also diminished. Histologically, the regressive changes in the treated tumors were due to the enhancement of apoptosis (programmed cell death) of tumor cells. Membrane receptor assays showed that LH-RH binding sites were down-regulated in tumor cells after treatment with SB-75 or D-Trp6-LH-RH. The results indicate that the antagonist SB-75, released from sustained delivery systems, can inhibit the growth of MCF-7 MIII tumors as effectively as the agonist D-Trp6-LH-RH, but more rapidly. In view of its immediate blockade of the pituitary-gonadal axis and the absence of side effects, the LH-RH antagonist SB-75 might be considered as a possible new hormonal agent for the treatment of breast cancer.

L46 ANSWER 39 OF 41 MEDLINE
AN 92115111 MEDLINE
TI Recovery of pituitary-gonadal function in male and female rats after prolonged **administration** of a potent antagonist of luteinizing hormone-releasing hormone (SB-75).
AU Bokser L; Srkalovic G; Szepeshazi K; Schally A V
CS Endocrine, Polypeptide and Cancer Institute, VA Medical Center, New Orleans, La..
NC CA 40003 (NCI)
CA 40004 (NCI)
SO NEUROENDOCRINOLOGY, (1991 Aug) 54 (2) 136-45.
Journal code: NY8. ISSN: 0028-3835.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 9204
AB The reversibility of the antifertility effects induced by long-term **administration** of the LH-RH antagonistic analog [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]-LH-RH (SB-75) was investigated in male and female rats. Male rats were implanted with osmotic minipumps releasing 50 micrograms of SB-75/day for 60 days. The control rats were implanted with minipumps containing only vehicle. The treatment with the antagonist caused a significant decrease in the weights of the testes, seminal vesicles and ventral prostates (p less than 0.01) and reduced serum LH and testosterone levels (p less than 0.01). The histology of the testes from the treated rats showed that spermatogenesis was totally depressed. No mature elongated or round spermatids were found in the seminiferous tubules, spermatocytes being the most advanced germ cell form in 100% of the testicular tubules. These changes indicate that a total spermatogenetic arrest occurred in the treated animals. Ninety days after cessation of treatment with the LH-RH antagonist, there was a complete recovery of the weights of the testes, seminal vesicles and ventral prostates and LH and testosterone returned to control levels. Histological studies revealed a complete recovery of spermatogenesis, with 99.2% of seminiferous tubules containing mature elongated spermatids. Immediately after the discontinuation of treatment with SB-75, a significant down-regulation of the pituitary LH-RH receptors was found, but 90 days later, this phenomenon was completely reversed. Female rats were injected every 3 weeks for 6 weeks with SB-75 microcapsules, at a dose calculated to release 27 micrograms/day of the antagonist. The treatment with SB-75 disrupted the normal estrous cycle. Body weights were not affected, but **ovarian** and uterine weights were significantly decreased (p less than 0.01 and p less than 0.05, respectively) in the animals treated with the antagonist. Treated rats had significantly lower LH (p less than 0.05) and estradiol (p less than 0.01) levels than controls. The histology of the **ovaries** from the SB-75-treated group showed that the ratio of small to large maturing follicles increased significantly (p less than 0.01) and corpora lutea were absent. Two months after the cessation of treatment, a complete recovery in the organ weights and in hormonal levels was observed and no histological differences were found between the **ovaries** in treated and untreated rats. These collective results indicate that the suppression of gonadal function induced by the treatment with LH-RH antagonist SB-75 is completely reversible both in male and female animals.(ABSTRACT TRUNCATED AT 400 WORDS)

L46 ANSWER 40 OF 41 MEDLINE DUPLICATE 24
AN 90189216 MEDLINE
TI Growth inhibition of mouse MXT mammary tumor by the luteinizing hormone-releasing hormone antagonist SB-75.
AU Szende B; Srkalovic G; Groot K; Lapis K; Schally A V
CS Endocrine, Polypeptide and Cancer Institute, Veterans Administration Medical Center, New Orleans, LA 70146..
NC CA-40004 (NCI)
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1990 Mar 21) 82 (6) 513-7.
Journal code: J9J. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9006

AB Female BDF1 mice bearing MXT mammary adenocarcinomas were treated for 3 weeks with the luteinizing hormone-releasing hormone (LH-RH) antagonist [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]-LH-RH (SB-75), with the agonist D-Trp6-LH-RH, with tamoxifen (5 micrograms per animal per day subcutaneously), with the combination of D-Trp6-LH-RH and tamoxifen, or by surgical **ovariectomy**. SB-75 and D-Trp6-LH-RH were **administered** in the form of microcapsules releasing 25 micrograms/day. The reduction in tumor weights after treatment with SB-75, D-Trp6-LH-RH, D-Trp6-LH-RH plus tamoxifen, or **ovariectomy** was 84%, 64%, 33%, and 67%, respectively. Tamoxifen alone was ineffective. Histologically, the regressive changes in the treated tumors were characteristic of apoptosis (programmed cell death). In view of its potency and its immediate inhibitory effect, the LH-RH antagonist SB-75 should be considered as a possible new hormonal agent for the treatment of breast cancer.

L46 ANSWER 41 OF 41 TOXLIT
AN 90:43813 TOXLIT
DN CA-112-172406J
TI Development of radioimmunoassay for a potent luteinizing hormone-releasing hormone antagonist. Evaluation of serum levels after injection of [Ac-3-(2-naphthyl)-D-Ala1, D-Phe(pCl)2, 3-(3-pyridyl)-D-Ala3, D-Cit6, D-Ala10] LHRH.
AU Csernus VJ; Szende B; Groot K; Redding TW; Schally AV
CS VA Med. Cent., Endocr. Polypept. Cancer Inst., New Orleans
SO Arzneim.-Forsch, (1990). Vol. 40, No. 2, pp. 111-18.
CODEN: ARZNAD. ISSN. 0004-4172.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 112:172406
EM 9006
AB To facilitate pharmacokinetic studies necessary for exptl. and clin. investigation of the title LH-RH analog (SB-75; I) a highly sensitive and specific RIA was developed. The antibody against SB-75 was generated in rabbits. No cross-reactions were detected with several natural peptides and analogs. The sensitivity of the assay is 0.6 pg/tube. The RIA is suitable for direct detn. of SB-75 in 20 muL serum. Two lots of SB-75 microcapsules exhibited different pharmacokinetic release patterns. Single i.m. injection of 20 mg SB-75 microcapsules, PLGA batch No. 001, into female rats maintained elevated serum SB-75 levels for 3 wk. The suppression of LH secretion during this period was indicated by histol. findings. The **ovaries** in the treated group were polyfollicular and no corpora lutea were present, indicating a prolonged **ovarian** inactivity due to LH deprivation. There was also a redn. in the size and wt. of the **ovaries** (40.4 mg vs. 66.7 mg for controls). The **administration** of SB-75 microcapsules, PLGA batch Nr. 002, to male rats produced high serum SB-75 levels for about 10 days, but an elevation in SB-75 values was maintained for 29 days. Serum testosterone (T), LH, and prolactin levels were reduced. A greater depression in serum T occurred on days 2-7, than on days 14-24, indicating that this batch exerted maximal effects during the 1st 7 days. Histol. examns. of the testicles revealed signs of impaired spermatogenesis. Prostate histol. in these rats also indicated reduced activity. Thus, improved sustained delivery formulations should be capable of maintaining therapeutic levels of the antagonist for several weeks.

The RIA developed should be of value for monitoring SB-75 levels during long-term therapy.

FILE 'USPATFULL' ENTERED AT 16:38:23 ON 03 SEP 1997
CA INDEXING COPYRIGHT (C) 1997 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Aug 1997 (19970826/PD)
FILE LAST UPDATED: 29 Aug 1997 (970829/ED)
HIGHEST PATENT NUMBER: US5661848
CA INDEXING IS CURRENT THROUGH 29 Aug 1997 (970829/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 26 Aug 1997 (19970826/PD)
REVISED CLASS FIELDS (/NCL) CURRENT THROUGH: JUN 1997
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: APR 1997

>>> Page images are available for patents from 1/1/94. Current <<<
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>>> Complete CA file indexing for chemical patents (or equivalents) <<<
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>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4, <<<
>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
            4 L1
            5 CETRORELIX
        23675 FERTIL?
         1025 INFERTIL?
         7427 OVAR?
        60854 REPRODUCT?
          556 REPROD##
         1550 OVULAT?
         2030 GYNECOL?
        97654 ADMIN?
L47         2 L31 AND ADMIN?

=> d 1-2 bib abs; fil ca,caplus; s l45

L47  ANSWER 1 OF 2  USPATFULL
AN     93:25009  USPATFULL
TI     LHRH antagonists
IN     Schally, Andrew V., Metarie, LA, United States
       Bajusz, Sandor, New Orleans, LA, United States
PA     The Administrators of the Tulane Educational Fund, New Orleans,
       LA, United States (U.S. corporation)
PI     US 5198533  930330
AI     US 88-197153  880523 (7)
DCD    20060124
RLI    Continuation-in-part of Ser. No. US 87-74126, filed on 17 Jul
```

1987, now abandoned
DT Utility
EXNAM Primary Examiner: Cashion, Jr., Merrell C.; Assistant Examiner: Wessendof, T. D.
LREP Behr, Omri M.; McDonald, Matthew J.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 927
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention deals with LHRH antagonists which possess improved water solubility and while having the high antagonist potency of the basic peptides, are free of the edematogenic effects. These compounds are highly potent in inhibiting the release of gonadotropins from the pituitary gland in mammals, including humans.

The compounds of this invention are represented by the formula

X--R.sup.1 --R.sup.2 --R.sup.3 --Ser--Tyr--R.sup.6 --Leu--Arg--Pro--R.sup.10 --NH.sub.2

wherein

X is an acyl group derived from straight or branched chain aliphatic or alicyclic carboxylic acids having from 1 to 7 carbon atoms, or H.sub.2 N--CO,

R.sup.1 is D-- or L--Pro, D-- or L--.DELTA..sup.3 --Pro, D--Phe, D--Phe(4--H1), D--Ser, D--Thr, D--Ala, D--Nal(1) or D--Nal (2),

R.sup.2 is D--Phe or D--Phe(4--C1)

R.sup.3 is D--Trp, D--Phe, D--Pal(3), D--Nal(1) or D--Nal(2),

R.sup.6 is D--Cit, D--Hci, D--Cit(Q) or D--Hci(Q) and

R.sup.10 is Gly or D--Ala

where Q is lower alkyl of 1-3 carbon atoms and H1 is fluoro, chloro or bromo, and the pharmaceutically acceptable acid addition salts thereof and methods of use pertaining to these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L47 ANSWER 2 OF 2 USPATFULL
AN 89:6035 USPATFULL
TI LHRH antagonists
IN Schally, Andrew V., 5025 Kawanne Ave., Metarie, LA, United States 70002
Bajusz, Sandor, 10501 Curran Blvd. #5W, New Orleans, LA, United States 70127
PI US 4800191 890124
AI US 87-74126 870717 (7)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Behr, Omri M.
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 820
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention deals with LHRH antagonists which possess improved water solubility and while having the high antagonist potency of the basic peptides, are free of the edematogenic effects. These compounds are highly potent in inhibiting the release of gonadotropins from the pituitary gland in mammals, including humans.

The compounds of this invention are represented by the formula

X-R.sup.1 -R.sup.2 -R.sup.3 -Ser-Tyr-R.sup.6 -Leu-Arg-Pro-R.sup.10 -NH.sub.2

wherein

X is an acyl group derived from straight or branched chain aliphatic or alicyclic carboxylic acids having from 1 to 7 carbon atoms,

R.sup.1 is D- or L-Pro, D- or L- .DELTA. .sup.3 -Pro, D-Phe, D-Phe(4-H1), D-Ser, D-Thr, D-Ala, D-Nal (1) or D-Nal (2),

R.sup.2 is D-Phe or D-Phe(4-H1)

R.sup.3 is D-Trp, D-Phe, D-Pal, D-Nal(1) or D-Nal (2),

R.sup.6 is D-Cit, D-Hci, D-Cit(Q) or D-Hci(Q) and

R.sup.10 is Gly or D-Ala

where Q is lower alkyl of 1-3 carbon atoms and H1 is fluoro, chloro or bromo,

and the pharmaceutically acceptable acid addition salts thereof and methods of use pertaining to these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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'L4' NOT FOUND
'L4' NOT FOUND

=> s l4 and gynecol?
L48 2 FILE CA
L49 2 FILE CAPLUS

TOTAL FOR ALL FILES
L50 4 L4 AND GYNECOL?

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=> s l50 not l16
L51             1 FILE CA
L52             1 FILE CAPLUS

TOTAL FOR ALL FILES
L53             2 L50 NOT L16

=> dup rem l53
PROCESSING COMPLETED FOR L53
L54             1 DUP REM L53 (1 DUPLICATE REMOVED)

=> d .bevstr

L54  ANSWER 1 OF 1  CA  COPYRIGHT 1997 ACS                DUPLICATE 1
AN   117:104637  CA
TI   Evaluation of luteinizing hormone-releasing hormone antagonistic
     activity in vivo
AU   Csernus, Valer J.; Schally, Andrew V.
CS   Endocr. Polypept. Cancer Inst., Vet. Adm. Med. Cent., New Orleans,
     LA, 701460, USA
SO   Proc. Natl. Acad. Sci. U. S. A. (1992), 89(13), 5759-63
     CODEN: PNASA6; ISSN: 0027-8424
DT   Journal
LA   English
AB   Antagonistic analogs of LH-RH belong to a class of compds. that can
     be utilized for treatment of some hormone-dependent cancers and
     gynecol. disorders.  LH-RH analogs were tested for LH-RH
     antagonistic activity in the dispersed pituitary cell superfusion
     system.  This fast, reliable, and dynamic system made it possible
     not only to evaluate the relatiive amts. of an analog required for
     suppression of the LH-releasing activity of exogenous LH-RH, but
     also provided quant. data on dynamic interactions between the LH-RH
     analog, LH-RH receptors, and LH secretion.  Three exptl. paradigms
     were used: (1) LH-RH responses after preincubation with the
     antagonist, (2) pulsatile, simultaneous infusion of LH-RH and the
     antagonistic analog, and (3) effects of the analogs on ongoing,
     continuous LH secretion induce by prolonged stimulation with LH-RH.
     The suppression of the LH-RH-induced LH release was more effective
     and longer lasting when the cells were preincubated with the
     antagonistic analog before the LH-RH stimulation than in the case of
     simultaneous exposure.  Not only the potency, but also the time of
     onset and the duration, of the LH release-suppressing activity
     varied with the different peptides used, resulting in different
     shapes of response curves.  From the accurate data obtained in this
     dynamic system, quant. parameters of the in vivo interactions
     between the antagonists and LH-RH on the LH-RH receptor could be
     calcd.
IT   120287-85-6
     RL: BIOL (Biological study)
        (LH-RH activity antagonism by)

=> fil reg
FILE 'REGISTRY' ENTERED AT 16:40:28 ON 03 SEP 1997
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STRUCTURE FILE UPDATES:  29 AUG  97  HIGHEST RN 193400-04-3
DICTIONARY FILE UPDATES: 02 SEP  97  HIGHEST RN 193400-04-3
                              Searcher :  Shears  308-4994
```

TSCA INFORMATION NOW CURRENT THROUGH DECEMBER 1996

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Query 2
LHRH and gonadotropin

```
=> e gonadotropin/cn 5
E1            1     GONADOTROPIC HORMONE .BETA.2 SUBUNIT (ONCORHYNCHUS MAS
                    OU)/CN
E2            1     GONADOTROPIC HORMONES, PITUITARY/CN
E3            0 --> GONADOTROPIN/CN
E4            1     GONADOTROPIN (ACANTHOPAGRUS LATUS CLONE SC-1 .ALPHA.-S
                    UBUNIT PRECURSOR)/CN
E5            1     GONADOTROPIN (CHLAMYDOMONAS REINHARDTI CLONE 28-3 PHOT
                    OSYSTEM I 11.0-KILODALTON SUBUNIT)/CN

=> s gonadotropin ?/cn
L55          75 GONADOTROPIN ?/CN

=> e "luteinizing hormone-releasing hormone"/cn 5
E1            1     LUTEINIZING HORMONE-RELEASING FACTOR-ASSOCIATED PEPTID
                    E-II (ONCORHYNCHUS NERKA)/CN
E2            1     LUTEINIZING HORMONE-RELEASING FACTOR-II (ONCORHYNCHUS
                    NERKA PRECURSOR)/CN
E3            1 --> LUTEINIZING HORMONE-RELEASING HORMONE/CN
E4            1     LUTEINIZING HORMONE-RELEASING HORMONE ENDOPEPTIDASE/CN
E5            1     LUTEINONE/CN

=> s e3; fil ca,caplus
L56           1 "LUTEINIZING HORMONE-RELEASING HORMONE"/CN


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=> s (l55 or gonadotrop?) and (l56 or lhrh or lh(w)rh or lutein?(1w)releas?(w)hormone#)
L57        7646 FILE CA
L58        7657 FILE CAPLUS

TOTAL FOR ALL FILES
L59       15303 (L55 OR GONADOTROP?) AND (L56 OR LHRH OR LH(W) RH OR LUTEI
                N?(1W) RELEAS?(W) HORMONE#)

=> d que stat
L55           75 SEA FILE=REGISTRY ABB=ON  PLU=ON  GONADOTROPIN ?/CN
L56            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LUTEINIZING HORMONE-RE
                  LEASING HORMONE"/CN
L60         7795 SEA FILE=CA ABB=ON  PLU=ON  (L55 OR GONADOTROP?) AND (L56
                  OR LHRH OR (LH OR LUTEIN? HORMON)(W)(RH OR RELEAS?(W)HOR
                  MONE#) OR GONADORELIN)
L61         7806 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L55 OR GONADOTROP?) AND
                  (L56 OR LHRH OR (LH OR LUTEIN? HORMON)(W)(RH OR RELEAS?(W
                  )HORMONE#) OR GONADORELIN)
```

Searcher : Shears 308-4994

```
L62        15601 SEA (L55 OR GONADOTROP?) AND (L56 OR LHRH OR (LH OR LUTEI
                 N? HORMON)(W)(RH OR RELEAS?(W) HORMONE#) OR GONADORELIN)

=> s l62 and (fertil? or infertil? or ovar? or reproduct? or reprod## or ovulat? or
gynecol?)
L63         3633 FILE CA
L64         3641 FILE CAPLUS

TOTAL FOR ALL FILES
L65         7274 L62 AND (FERTIL? OR INFERTIL? OR OVAR? OR REPRODUCT? OR RE
                 PROD## OR OVULAT? OR GYNECOL?)

=> s l65 and admin?
L66         1242 FILE CA
L67         1244 FILE CAPLUS

TOTAL FOR ALL FILES
L68         2486 L65 AND ADMIN?

=> d que
L55           75 SEA FILE=REGISTRY ABB=ON  PLU=ON  GONADOTROPIN ?/CN
L56            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LUTEINIZING HORMONE-RE
                 LEASING HORMONE"/CN
L90          272 SEA FILE=CA ABB=ON  PLU=ON  (L55 OR GONADOTROP?)(L)((L56
                 OR LHRH OR (LH OR LUTEIN? HORMON)(W)(RH OR RELEAS?(W)HORM
                 ONE#) OR GONADORELIN)(3A)ANTAGON?)
L91          273 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L55 OR GONADOTROP?)(L)((
                 L56 OR LHRH OR (LH OR LUTEIN? HORMON)(W)(RH OR RELEAS?(W)
                 HORMONE#) OR GONADORELIN)(3A)ANTAGON?)
L92          545 SEA (L55 OR GONADOTROP?)(L)((L56 OR LHRH OR (LH OR LUTEIN
                 ? HORMON)(W)(RH OR RELEAS?(W) HORMONE#) OR GONADORELIN)(3
                 A) ANTAGON?)
L93          116 SEA FILE=CA ABB=ON  PLU=ON  L90(L)(FERTIL? OR INFERTIL? O
                 R OVAR? OR REPRODUCT? OR REPROD## OR OVULAT? OR GYNECOL?)

L94          117 SEA FILE=CAPLUS ABB=ON  PLU=ON  L91(L)(FERTIL? OR INFERTI
                 L? OR OVAR? OR REPRODUCT? OR REPROD## OR OVULAT? OR GYNEC
                 OL?)
L95          233 SEA L92(L)(FERTIL? OR INFERTIL? OR OVAR? OR REPRODUCT? OR
                  REPROD## OR OVULAT? OR GYNECOL?)
L96           36 SEA FILE=CA ABB=ON  PLU=ON  L93(L)ADMIN?
L97           37 SEA FILE=CAPLUS ABB=ON  PLU=ON  L94(L)ADMIN?
L98           73 SEA L95(L) ADMIN?

=> s l98 not (l16 or l53)
L99          33 FILE CA
L100         33 FILE CAPLUS

TOTAL FOR ALL FILES
L101         66 L98 NOT (L16 OR L53)

=> dup rem l101
PROCESSING COMPLETED FOR L101
L102          33 DUP REM L101 (33 DUPLICATES REMOVED)

=> d 1-33 bib abs

L102 ANSWER 1 OF 33  CA  COPYRIGHT 1997 ACS            DUPLICATE 1
AN   127:117503  CA
TI   Effects of progesterone on the secondary surge of
```

follicle-stimulating hormone in the rat
AU Tebar, M.; Uilenbroek, J. Th. J.; Kramer, P.; van Schaik, R. H. N.; Lierikx, C. D. J.; Ruiz, A.; de Jong, F. H.; Sanchez-Criado, J. E.
CS Dep. Physiol., Fac. Med., Univ. Cordoba, Spain
SO Biol. Reprod. (1997), 57(1), 77-84
CODEN: BIREBV; ISSN: 0006-3363
PB Society for the Study of Reproduction
DT Journal
LA English
AB In the cyclic rat, the secondary surge of FSH on estrus appears to depend on the LH surge-induced fall in serum concns. of inhibin. To investigate the involvement of progesterone in the regulation of the secondary surge of FSH, 4-day cyclic rats were treated in proestrus with an **antagonist** of **LH-RH** (LHRHant) and with an **ovulatory** dose of ovine (o) LH, progesterone, the antiprogestin RU486, or the combination of RU486 and oLH. Serum concns. of **gonadotropins** and inhibin at 1830 h on proestrus and at 0030 h on estrus were detd.., and the expression of inhibin/activin subunit mRNAs in the **ovary** at 0030 h on estrus was analyzed by in situ hybridization. Rats receiving saline showed low expression of .alpha.-, .beta.A-, and .beta.B-subunit mRNAs in the **ovary** and low serum levels of inhibin in conjunction with the elevated serum concns. of FSH on estrus. **Administration** of LHRHant blocked the decrease in the synthesis and secretion of inhibin and abolished the FSH secondary surge, whereas the injection of oLH prevented these effects. Exogenous progesterone, compared with LHRHant injection, increased .alpha.-, .beta.A-, and .beta.B-subunit mRNA hybridization intensity in the **ovary** and serum inhibin immunoreactivity, and also restored, in part, the surge of FSH on estrus. The antiprogestin RU486 did not modify the effect of oLH on either inhibin/activin subunit mRNAs in the **ovary** or serum levels of inhibin, but blocked the FS surge. These results indicate that, in the cyclic rat, (1) the secretion of progesterone on proestrous afternoon, induced by the LH surge, is not involved in the fall of **ovarian** inhibin synthesis and secretion; and (2) in combination with a drop in serum inhibin, stimulatory action of progesterone on another factor, possibly pituitary activin, could be necessary to elicit a complete secondary surge of FSH.

L102 ANSWER 2 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 125:133087 CA
TI Recombinant FSH-induced follicle development in immature rats treated with an LH-RH antagonist: a direct effect of RU 486 on follicular atresia
AU Uilenbroek, J. Th. J.; Kramer, P.; van Leeuwen, E. C. M.; Karels, B.; Timmerman, M. A.; de Jong, F. H.; de Leeuw, R.
CS Dep. Endocrinol. Reproduction, Erasmus Univ. Rotterdam, Rotterdam, 3000 DR, Neth.
SO J. Endocrinol. (1996), 150(1), 85-92
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB To investigate whether the progesterone antagonist RU 486 has a direct effect on **ovarian** function, it was **administered** to immature female rats rendered hypogonadotrophic by **administration** of an **LH-RH antagonist** and in which follicle development was stimulated by recombinant human FSH (recFSH). In the first expts. the effects of **LH-RH antagonist**

and recFSH on follicle growth were evaluated. Female rats of 22 days of age were injected with an **LH-RH antagonist** (Org 30276; 500 .mu.g/100 g body wt.) every other day. This treatment resulted in a 10-fold decrease in serum LH concns. and a 2-fold decrease in serum FSH concns. at day 30 and caused a redn. in the no. and size of antral follicles. Treatment with recFSH (Org 32489) twice daily from day 26 for 4 days in a total dose ranging from 5 to 20 IU/animal increased the no. and size of antral follicles in a dose-related manner and resulted after 20 IU recFSH in a 10-fold increase in the concn. of inhibin in serum and **ovaries** at day 30. Once it was established that **LH-RH antagonist** treatment in immature rats could be used to study the effects of **gonadotropins** or steroids on follicle function, this animal model was used to study the effects of RU 486 on the **ovary**. RU 486 was **administered** (twice daily for 4 days, 1 mg/injection) to **LH-RH antagonist**-treated rats in which follicular growth and differentiation were stimulated by 10 IU recFSH or by 10 IU recFSH plus 0.5 IU human chorionic **gonadotropin** (hCG). RU 486 had no effect on circulating levels of LH and FSH, but stimulated follicular atresia both in rats treated with recFSH alone and in rats treated with recFSH and hCG. Inhibin concns. both in serum and **ovaries** were significantly increased after hCG treatment. RU 486, however, did not increase inhibin in the rats treated with recFSH and in those treated with recFSH and hCG. In summary, the present study has demonstrated that (1) immature rats treated with an **LH-RH antagonist** can be used to study the effects of **gonadotropins** and steroids on follicular function and (2) RU 486 has a direct stimulatory effect on follicular atresia.

L102 ANSWER 3 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 123:189355 CA
TI Ovulation control by regulating nitric oxide levels
IN Garfield, Robert E.; Yallampalli, Chandrasekhar
PA Board of Regents, University of Texas System, USA
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
PI WO 9515753 A1 950615
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-US14133 941208
PRAI US 93-165309 931210
DT Patent
LA English
AB Inhibition of **ovulation** in a female may be achieved by **administering** a nitric oxide synthase inhibitor, alone or in combination with one or more of a progestin, an estrogen, and an **LH-RH antagonist**, thereby preventing conception. The stimulation of **ovulation** in a female may be achieved by **administering** a nitric oxide source, optionally in further combination with one or more of clomiphene, a **gonadotropin**, and an LH-RH agonist. Thus, 27 days old immature rats were injected with 4 IU of pregnant mare's serum **gonadotropin** on day on. Two days later rats were injected with 40 mg of NG-nitro-L-arginine Me ester at 12 AM and 3 PM and animals were sacrificed one day later and examd. for the

ovulatory response by counting the no. of Graafian follicles 3 and corpora lutea 5 in the **ovaries**. The no. of Graffian follicles and corpora lutea was 9.7 and 0.7 resp. as compared to 1.0 and 10.0 for the controls.

L102 ANSWER 4 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 4
AN 123:306862 CA
TI Effect of different treatments on hormone secretion and cystic ovarian morphology in the rat treated with RU486
AU Ruiz, A.; Aguilar, R.; Tebar, M.; Gaytan, F.; Sanchez-Criado, J. E.
CS Facultad de Medicina, Universidad de Cordoba, 14004, Spain
SO Endocrinologia (Barcelona) (1995), 42(5), 150-5
CODEN: ENDCDP; ISSN: 0211-2299
DT Journal
LA French
AB Rats treated with the antiprogestagen RU486 (RU) present a cystic **ovarian** picture compatible endocrinol. and morphol. with the human polycystic **ovarian** syndrome (PCOS). The **administration** of an **antagonist** of **LHRH** to rats deprived of the actions of progesterone by the antiprogestagen, reduced the high serum levels of LH, testosterone (T) and estradiol (E2), as well as the quotients LH/FSH and T/E2; the **ovary** decreased in size and presented a lower no. of cysts, a lesser degree of atresia and a reactivation of follicular growth. A similar effect was obsd. in the rats treated with the antiestrogen tamoxifen. The **administration** of the antiandrogen flutamide increased the endocrinol. changes, whereas it decreased, in part, the morphol. ones. The redn. in the serum levels of prolactin by the dopaminergic agonist bromocriptine failed to normalize the secretion of **gonadotropins** and the prodn. of **ovarian** steroids, although the **ovary** showed a decrease in the no. of cysts and the degree of atresia, as well as an increase in follicular growth. Finally, the **administration** of human FSH (hFSH) to rats treated with RU increased the peripheral levels of E2 without altering the remaining endocrine parameters. However, hFSH originated an important decrease in the degree of atresia and an intense reactivation in follicular growth in the **ovary**. Similar therapeutic measures used in patients with polycystic **ovarian** syndrome (PCOS) produce endocrinol. and morphol. changes very like those described above in the rats treated with RU. This, together with the existing similarities between the anovulatory cystic picture in the animal model and the patients with PCOS, confirms the value of rats treated with the antiprogestagen RU486 as a model for studying this disease, as well as the importance of progesterone in developing and maintaining the condition of **ovarian** cysts.

L102 ANSWER 5 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 5
AN 122:231120 CA
TI Evidence of a permissive effect of extra-ovarian steroids on the release of FSH at early estrus in rats lacking inhibin secretion or action
AU Tebar, Maria; Bellido, Carmina; Sanchez-Criado, Jose E.
CS Faculty Medicine, University of Cordoba, Cordoba, 14004, Spain
SO Neuroendocrinol. Lett. (1995), 17(1), 21-7
CODEN: NLETDU; ISSN: 0172-780X
DT Journal
LA English
AB The **administration** (s.c.) of 1 mg of a **LHRH** **antagonist** (LHRHa) to 4-day cyclic rats at 0900 h in

proestrus blocked the preovulatory (proestrous 1830 h) release of **gonadotropins** (LH and FSH) and abolished the secondary (estrous 0200 h) release of FSH. The **administration** (s.c.) of 4 mg of either anti-progestagen RU486 or anti-progestagen ZK299 at 0900 h in proestrus blunted the preovulatory release of **gonadotropins** and abolished the secondary release of FSH. The effect of the LHRHa on the secondary surge of FSH in cyclic rats was totally reversed by an **ovulatory** (s.c.) injection (10 IU) of hCG at 1700 h in proestrus. Injections of 3, 5 or 10 mg (s.c.) of progesterone at 1500 h in proestrus or of 0.5 mL (i.v.) of an anti-inhibin serum at 1900 h in proestrus alone reversed, although only in part, the effect of LHRHa on the serum concn. of FSH at 0200 h in estrus. The combination of progesterone and anti-inhibin serum injections to LHRHa-treated rats completely restored the secretion of FSH at early estrus. The removal of **ovarian** progesterone and inhibin by **ovariectomy** (OVX) at 1500 h on proestrus did not affect the serum concn. of FSH at 0200 h on estrus either in oil- or RU486-treated rats. The injection of progesterone to OVX-rats did not affect the serum concns. of FSH or LH at 0200 h in estrus. These combined observations suggest that, in the rat, the preovulatory LH-dependent drop in **ovarian** inhibin secretion, together with the actions of steroids, which can be blocked by the **administration** of either RU486 or ZK299, during proestrous afternoon and evening allow the secondary release of FSH during early estrus. These steroids (progesterone and/or glucocorticoids) come from extra-**ovarian** tissues (most probably the adrenal glands).

L102 ANSWER 6 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 6
AN 121:196402 CA
TI Mechanisms of reproductive deficiency in male rats treated neonatally with a gonadotropin-releasing hormone antagonist
AU Pinilla, L.; Garnelo, P.; Tena-Sempere, M.; Gaytan, F.; Aguilar, E.
CS Dep. Physiology, Univ. Cordoba, Cordoba, Spain
SO J. Endocrinol. (1994), 142(3), 517-25
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB It is well known that males injected neonatally with estradiol or antiserum or antagonists (ANT) against gonadotropin-releasing hormone (GnRH) show multiple reproductive disorders. In the present work, in males treated neonatally with GnRH-ANT, we have analyzed: (1) whether the impairment of reproductive function can be blocked by simultaneous treatment with gonadotropins; (2) the possible differences in the effects of GnRH-ANT injected before or after the proliferation of Sertoli cells which takes place between days 1 and 15 of age; and (3) the mechanism(s) for the increased FSH secretion obsd. in adulthood. Exptl. designs included: administration of GnRH-ANT between days 1 and 16 or 15 and 30 of age; simultaneous administration of gonadotropins and GnRH-ANT to neonatal males; and measurement of FSH secretion after orchidectomy or specific destruction of Leydig cells with ethylene dimethane sulfonate (EDS) in adult males treated neonatally with GnRH-ANT. The principal new data presented in our studies are the following: (1) delayed puberty was obsd. not only in males injected neonatally with GnRH-ANT, but also in those injected with gonadotropins or with GnRH-ANT and gonadotropins; (2) the decreased fertility and increased FSH secretion obsd. in adult males treated neonatally with GnRH-ANT were normalized by simultaneous administration of GnRH-ANT and

gonadotropins; and (3) the increased FSH secretion in adult males treated neonatally with GnRH-ANT remained after EDS or orchidectomy, suggesting that mechanisms other than decreased inhibin secretion were involved in the increased secretion of FSH.

L102 ANSWER 7 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 7
AN 120:52356 CA
TI The chronic intracerebroventricular infusion of interleukin-1.beta. alters the activity of the hypothalamic-pituitary-gonadal axis of cycling rats. II. Induction of pseudopregnant-like corpora lutea
AU Rivier, Catherine; Erickson, Gregory
CS Clayton Found. Lab. Pept. Biol., Salk Inst., La Jolla, CA, 92037, USA
SO Endocrinology (1993), 133(6), 2431-6
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
AB The acute **administration** of interleukin-1.beta. (IL-1.beta.) into the brain ventricles of rats has been shown to cause a significant decrease in plasma LH levels, a phenomenon primarily mediated through inhibition of LH-RH release. However, there are no studies of the long-term consequences of IL-1.beta. injected intracerebroventricularly on the hypothalamic-pituitary-gonadal axis. In particular, the authors became interested in detg. whether IL-1.beta. exerts deleterious effects on **reproductive** parameters, and to what extent they might be caused by a lowering of circulating **gonadotropins**. In the present expts., the authors therefore investigated the effects of the infusion of IL-1.beta. to intact cycling female rats and compared them to those obsd. in rats injected with a potent **LH-RH antagonist**. Although blockade of LH-RH receptors caused a modest and delayed inhibition of progesterone (P4) secretion, infusion of IL-1.beta. (4 ng/h for 4-6 days) was accompanied by persistent and significant increases in plasma P4 levels. In these rats, the pattern of PRL release was erratic, with low values during the morning and generally extremely elevated values during the night. The vol. of the corpora lutea-I (CL-I) of rats exposed to IL-1.beta., but not to the vehicle or the **LH-RH antagonist**, was significantly increased, and the lutein cells showed extensive hypertrophy. These results indicate that prolonged infusion of IL-1.beta. into the brain of cycling rats blocks luteolysis in newly formed CL. These changes were not present in rats injected with the **LH-RH antagonist**, suggesting that they were not primarily related to decreases in **gonadotropin** secretion. The authors propose that the high plasma PRL levels may play a role in the changes in **ovarian** activity which the authors obsd., through other mechanisms, such as sustained increases in adrenal epinephrine and/or glucocorticoids, may also be involved. These findings indicate a novel role for central IL-1.beta. in the prevention of luteolysis and the transformation of the CL of the cycle into a CL of pseudopregnancy.

L102 ANSWER 8 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 8
AN 119:63800 CA
TI Differential gonadotropin responses to N-methyl-D,L-aspartate in metestrous, proestrous, and ovariectomized rats
AU Luderer, Ulrike; Strobl, Frank J.; Levine, Jon E.; Schwartz, Neena B.
CS Dep. Neurobiol. Physiol., Northwestern Univ., Evanston, IL, 60208,

USA
SO Biol. Reprod. (1993), 48(4), 857-66
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB Peripheral **administration** of N-methyl-D,L-aspartate (NMA), an analog of the excitatory amino acid aspartate, elicits LH and PRL release in rats, most likely by increasing endogenous releasing-hormone secretion. These expts. were carried out to assess the degree to which NMA stimulates FSH and to analyze the relationship between endocrine status and responsiveness to NMA in female rats, in contrast to male rats, as described in the companion paper. In expt. 1, estrous rats and diestrous rats and in expt. 2, estrous rats and rats **ovariectomized** (OVX) 8 days previously were fitted with atrial catheters and injected s.c. with 100 .mu.g of an **LHRH antagonist** or vehicle at 2100 h. Starting at 0900 h the next day (metestrus, proestrus, or Day 9 post-OVX), blood was withdrawn every 10 min for 3 h. Each animal received i.v. 5 mg NMA after the first hour and i.v. 500 ng LHRH after the second hour. NMA increased LH in metestrus and proestrus females, and **LHRH antagonist** blunted the increases. In OVX females, LH decreased after NMA. FSH was not affected by NMA in any group. PRL increased after NMA in proestrous and metestrous animals. LHRH caused surge-like LH and small FSH increases in vehicle groups; these increases did not differ in amplitude between intact and OVX animals and were blunted by pretreatment with **LHRH antagonist**. In expt. 3, 10 diestrous rats were fitted with atrial catheters and were serially bled at 2-h intervals from 1200 h on the following day (proestrus) until 0600 h on estrus morning. After the first sample the animals were injected s.c. with 0.2 mg/kg MK801, a noncompetitive NMA receptor antagonist, or with saline. Four of the 5 saline-treated animals exhibited surges of LH and FSH as well as elevated progesterone levels, with LH and progesterone peaking at 2000 h. Five of 5 MK801-treated animals failed to have elevated LH, FSH, or progesterone levels at any time point. These data demonstrate that LHRH mediates the LH response to NMA in rats and that endogenous NMA receptor binding may be necessary for the preovulatory **gonadotropin** surges. The lack of FSH responses to NMA during periods of low-level **gonadotropin** secretion suggests that physiol. increments in endogenous LHRH secretion sufficient to induce a pulse of LH are insufficient to stimulate pulse-like FSH release. Comparison of metestrus and proestrus NMA responses suggests that elevated proestrus estradiol levels do not enhance the releasability of LHRH by NMA, while the suppression of LH levels following NMA in OVX rats suggests that in the absence of **ovarian** feedback the inhibitory effects of NMA on LHRH release predominate over its stimulatory effects.

L102 ANSWER 9 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 9
AN 119:262901 CA
TI Inhibitory effect of a highly potent antagonist of LH releasing hormone (SB-75) on the pituitary gonadal axis in the intact and castrated rat
AU Ayalon, Daniel; Farhi, Yakob; Comaru-Schally, Anna Maria; Schally, Andrew Victor; Eckstein, Nachman; Vagman, Israel; Limor, Rona
CS Timsit Inst. Reprod. Endocrinol., Sourasky Med. Cent., Tel Aviv, Israel
SO Neuroendocrinology (1993), 58(2), 153-9
CODEN: NUNDAJ; ISSN: 0028-3835

DT Journal
LA English
AB The biol. potency of the new, highly potent antagonist [AC-D-Nal (2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10] LH-RH (SB-75) on the pituitary-gonadal system of female castrated and intact **ovulating** rats was tested. **Administration** of a single dose (50-100 .mu.g/kg) of the antagonist SB-75 inhibited effectively the elevated **gonadotropin** levels of castrated animals for 48 h. Pituitary LH and FSH contents were not affected by SB-75 treatment. When **administered** in the early afternoon on the proestrus day to intact cycling rats, SB-75 blocked the preovulatory LH surge as well as the primary and secondary FSH surges. However, the secondary FSH surge was not affected by SB-75 treatment when **administered** on the evening of proestrus, suggesting its independence from the LH-RH mechanism. A group of **ovariectomized** rats was chronically treated with the agonist D-Trp6-LH-RH after having been pretreated by **administration** of a single dose of the antagonist. The initial stimulatory release of LH and FSH initiated by injection of the LH-RH agonist was significantly reduced by pretreatment with the **LH-RH antagonist**. The authors conclude that the **LH-RH antagonist** SB-75 may be used effectively in the field of **reproductive** dysfunction and endocrinol. oncol. and may become an invaluable physiol. probe in studying the hormonal dynamics of the **reproductive** endocrine axis.

L102 ANSWER 10 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 10
AN 118:140111 CA
TI Changes in pituitary secretion during the early postnatal period and anovulatory syndrome induced by neonatal estrogen or androgen in rats
AU Pinilla, L.; Trimino, E.; Garnelo, P.; Bellido, C.; Aguilar, R.; Gaytan, F.; Aguilar, E.
CS Sch. Med., Univ. Cordoba, Spain
SO J. Reprod. Fertil. (1993), 97(1), 13-20
CODEN: JRPFA4; ISSN: 0022-4251
DT Journal
LA English
AB The following expts. were performed: (1) concns. of FSH, LH, and prolactin in plasma were measured at 2, 5, 8, 10, and 15 days in female Wistar rats treated on the first day of life with 100 .mu.g estradiol benzoate or vehicle; (2) females injected on day 1 with 100 .mu.g of estradiol benzoate or 1 mg of testosterone propionate and from day 1 to day 10 or 15 with FSH and LH were killed on day 90; (3) females injected from day 1 to day 10 or 15 with prolactin or vehicle were killed on day 90; (4) females injected on day 1 with estradiol benzoate and from day 1 to day 15 with a LH-RH agonist were killed on day 90; (5) groups of females injected on days 1, 4, 7, 10, 13, and 16 with an **LH-RH antagonist** were killed on day 90. Onset of puberty, vaginal cycles, organ wts. and hormonal plasma concns. were measured. Females treated on the first day of life with 100 .mu.g estradiol showed inhibition of **gonadotropin** secretion and stimulation of prolactin secretion during the neonatal period. Females injected on the first day of life with estradiol benzoate or testosterone propionate showed, in adulthood, anovulation, **ovarian** atrophy, reduced FSH plasma concns., increased prolactin plasma concns. and reduced pituitary prolactin content. These alterations were due neither to blocked **gonadotropin**

secretion nor to stimulated prolactin secretion obsd. immediately after steroid injection, since: (1) development of the anovulatory syndrome was not blocked by the **administration** of exogenous **gonadotropins** or LHRH-agonist; and (2) blockade of **gonadotropin** secretion immediately after birth with an **LHRH antagonist** or neonatal injection of prolactin did not induce the anovulatory syndrome. Thus, anovulation induced by **administration** of neonatal steroid was mediated neither by the early inhibition of **gonadotropin** secretion nor by the stimulation of prolactin secretion.

L102 ANSWER 11 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 11
AN 117:164198 CA
TI Properties of a potent LHRH antagonist (Org 30850) in female and male rats
AU Deckers, G. H. J.; De Graaf, J. H.; Kloosterboer, H. J.; Loozen, H. J. J.
CS Organon Sci. Dev. Group, Oss, 5340 BH, Neth.
SO J. Steroid Biochem. Mol. Biol. (1992), 42(7), 705-12
CODEN: JSBBEZ; ISSN: 0960-0760
DT Journal
LA English
AB Org 30850 (Ac-D-pClPhe1,2,D-Bal3,D-Lys6,D-Ala10-LHRH) is a novel **LHRH antagonist**, which is being developed for the treatment of hormone-dependent disorders. The activities of this compd. with respect to its endocrinol. properties and side-effects were tested in rats and the results were compared with one of the first **LHRH antagonists**: Ac-D-pClPhe1,2,D-Trp3,D-Arg6,D-Ala10-LHRH (Org 30276). A single s.c. dose of 0.3 .mu.g/kg Org 30850 **administered** to rats in proestrus inhibited **ovulation** in approx. 50% of the rats, whereas Org 30276 was approx. 4 times less potent. The effect of a single s.c. injection of Org 30850 on testosterone levels in young adult male rats was also studied. The **administration** of .gtoreq.250 .mu.g/kg Org 30850 decreased testosterone levels after 3 h; this effect lasted for at least 48 h. Treatment of female rats for 14 days with a daily dose of 12 .mu.g/kg Org 30850 decreased uterine and **ovarian** wts. At a daily dose of 50 .mu.g/kg Org 30850 completely suppressed estrous cycles and decreased serum estradiol and FSH levels. The LH levels were below the detection level in both control and treated animals on the (expected) second day of diestrus. Treatment of male rats for 14 days (25-200 .mu.g/kg) resulted in a dose-dependent redn. of the gonads, accessory sex organs, testosterone levels and **gonadotropins**. The decrease in gonadal function in both sexes was reversible since the females proved to be as **fertile** as the controls 6 wk after the last treatment and an almost complete recovery of the wt. of testes, seminal vesicles and ventral prostate was obsd. in the males 4 wk after cessation of treatment. In contrast to Org 30276, Org 30850 was only a slight irritant at the site of injection and did not cause edema in the extremities at a daily dose of up to 8 mg/kg in male rats. Thus, Org 30850 is a very potent **LH-RH antagonist** without edematous reactions and with a more favorable therapeutic index than Org 30276.

L102 ANSWER 12 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 12
AN 114:178505 CA
TI Antide-induced suppression of pituitary gonadotropin and ovarian steroid secretion in cynomolgus monkeys: premature luteolysis and prolonged inhibition of folliculogenesis following single treatment

AU Gordon, Keith; Williams, Robert F.; Danforth, Douglas R.; Hodgen, Gary D.
CS Jones Inst. Reprod. Med., East. Virginia Med. Sch., Norfolk, VA, 23510, USA
SO Biol. Reprod. (1991), 44(4), 701-6
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB **Administration** of high-doses of the **LH-RH antagonist** Antide to **ovariectomized** monkeys results in rapid, prolonged, and reversible inhibition of **gonadotropin** secretion. It was examd. whether similar long-term control would be manifested in the menstrual cycle of intact primates. Antide **administration** at a dose of either 3.0 or 18.0 mg/kg induced rapid suppression of bioassayable LH concns., pptg. a concurrent fall in serum progesterone concns. from .apprx.7 ng/mL on the day of injection to .apprx.0.5 ng/mL by 2 days post-treatment, resp. This Antide-induced luteolysis was accompanied by the premature onset of menses within 3 days. The next menses following Antide **administration** was delayed. Ultimately, folliculogenesis culminating in normal follicular-phase estradiol prodn., **ovulation**, and subsequent normal luteal-phase progesterone prodn. did occur in all treated monkeys. Menses resumed 54 and 75 days after treatment with 3.0 and 18.0 mg/kg Antide, resp. No allergic cutaneous or peripheral reactions were seen, even at the highest dose of Antide. Thus, the long duration of action of high-dose Antide reported earlier in **ovariectomized** monkeys is also demonstrated in intact primates. These findings, along with the apparent absence of histamine-release effects even at high doses, suggest that Antide is a GnRH antagonist deserving clin. evaluation for management of gonadal steroid-dependent endocrinopathies and for potential contraceptive applications.

L102 ANSWER 13 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 13
AN 114:157334 CA
TI Increased concentrations of immunoreactive inhibin during conception cycles in the marmoset monkey: suppression with an LHRH antagonist and cloprostenol
AU Webley, G. E.; Knight, P. G.; Given, A.; Hodges, J. K.
CS Comp. Physiol. Group, Inst. Zool., London, NW1 4RY, UK
SO J. Endocrinol. (1991), 128(3), 465-73
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB Peripheral concns. of immunoreactive (ir) inhibin have been measured during the **ovarian** cycle and early pregnancy in the marmoset monkey. Blood samples were taken (3/wk) during conception and non-conception cycles. Ir-inhibin was measured by RIA using an antiserum raised against a synthetic peptide fragment of the .alpha. subunit of human inhibin. Monomeric bovine .alpha. subunit and 32 kDa bovine inhibin were used as tracer and std. resp. In all animals low concns. of ir-inhibin were recorded during the follicular phase (40-60 .mu.g/L) of the cycle. After **ovulation**, ir-inhibin concns. increased but the peak concns. attained differed between conception and non-conception cycles. In non-pregnant animals ir-inhibin concns. reached a max. of 242 .mu.g/L on days 12/13 after **ovulation**. In pregnant animals ir-inhibin concns. were higher (1.8-fold) than in non-pregnant animals on days 8/9 after **ovulation**, and

reached a max. value of 636 .mu.g/L on days 20/21 after **ovulation**. **Administration** of an **LH-RH antagonist** during the luteal phase on days 6-8 after **ovulation** decreased progesterone and ir-inhibin concns. within 4 and 8 h, resp. This was prevented by coadministration with human chorionic **gonadotropin**. **Administration** of cloprostenol to pregnant animals between days 17 and 20 after **ovulation** halved the initial concns. of both inhibin and progesterone within 1.5 h. The increase in plasma ir-inhibin concns. in the luteal phase and the apparent similarity in control of ir-inhibin and progesterone supports a luteal source of ir-inhibin in both conception and non-conception cycles. The higher levels of ir-inhibin from days 8/9 after **ovulation** in conception cycles were not related to any detectable increase in peripheral concns. of chorionic **gonadotropin** and occurred at least 4 days before the expected time of implantation. This suggests a role for the conceptus in inhibin secretion which may involve the release of an embryo message before implantation.

L102 ANSWER 14 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 14
AN 114:36212 CA
TI Comparison of the luteolytic action of gonadotropin-releasing hormone antagonist and cloprostenol, and the ability of human chorionic gonadotropin and melatonin to override their luteolytic effects in the marmoset monkey
AU Webley, G. E.; Hodges, J. K.; Given, A.; Hearn, J. P.
CS MRC/AFRC Compar. Physiol. Group, Inst. Zool., London, NW1 4RY, UK
SO J. Endocrinol. (1991), 128(1), 121-9
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB The effects of the luteolytic and luteotropic agents cloprostenol human chorionic **gonadotropin** (hCG), and melatonin on the corpus luteum have been investigated in marmoset monkeys treated with an **LH-RH antagonist** to reduce endogenous LH secretion. This has allowed the effects of these agents to be investigated in the absence of the principal endogenous luteotropin. **Administration** of the **LH-RH antagonist** ([N-acetyl-D.beta.Nal1-D-pCl-Phe2-D-Phe3-D-Arg6-Phe7-Arg8-D-Ala10]NH2-LH-RH) or cloprostenol between days 7 and 11 after **ovulation** (preimplantation) resulted in luteolysis. A decrease in progesterone concns. had occurred by 4 h after **administration** of the **LH-RH antagonist**, and was preceded by a fall in LH concns. Co-**administration** of hCG with the **LH-RH antagonist** prevented the fall in progesterone. In contrast, **administration** of cloprostenol resulted in an immediate fall in progesterone concns., to less than half the initial level within 1 h; co-**administration** of hCG did not prevent the fall. **Administration** of hCG stimulated progesterone prodn. when given 8 h after the **LH-RH antagonist** but not after 24 h. Cloprostenol prevented the stimulation by hCG. Co-**administration** of melatonin with the **LH-RH antagonist** did not prevent the decrease in progesterone concns. Melatonin was also not effective in preventing the fall in progesterone induced by cloprostenol. However, co-**administration** of melatonin and cloprostenol between days 17 and 21 after **ovulation** (postimplantation) delayed the fall in progesterone seen with cloprostenol alone. Although the

LH-RH antagonist and cloprostenol have different sites of action, their effect is similar at the corpus luteum, i.e., in depriving the corpus luteum of luteotropic support. Melatonin may be able to influence the luteolytic action of cloprostenol, but its effect varies with the stage of the cycle. The physiol. role for such an action, if any, remains unknown.

L102 ANSWER 15 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 15
AN 112:229976 CA
TI Testicular weight, tubular diameter and number of Sertoli cells in rats are decreased after early prepubertal administration of an LHRH-antagonist; the quality of spermatozoa is not impaired
AU Van den Dungen, H. M.; Van Dieten, J. A. M. J.; Van Rees, G. P.; Schoemaker, J.
CS Dep. Obstet. Gynaecol., Vrije Univ., Amsterdam, Neth.
SO Life Sci. (1990), 46(15), 1081-9
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB To suppress **gonadotropin** secretion during the sensitive period in development of the testes, immature male rats were treated with an **antagonist** of **LH-RH** (ORG 30276) from postnatal days 6-15. Previously, it has been demonstrated that this treatment results in delayed pubertal development, decreased testicular wt., and impaired **fertility** and adult sexual behavior. In the present expts. it was investigated whether the decreased testicular wt. was correlated with morphol. changes in the testis. Also, by using an artificial insemination technique, the biol. activity of spermatozoa of adult male rats, treated during early prepuberty with the **LH-RH antagonist** (**LH-RH**-A), was tested. There was a decrease in the diam. of the testicular tubuli of LH-RH-A-treated rats. The no. of Sertoli cells per tubular cross-section was also smaller, but qual. no differences could be obsd. in the testis. All stages of maturation of the seminiferous epithelium were equally frequently represented in LH-RH-A-treated males compared with controls. Artificial insemination using spermatozoa obtained from the epididymis of LHRH-A-treated rats resulted in a pregnancy rate of 100%, similar to the control rate. Thus, the **infertility** in adult male rats, treated with an **antagonist** to **LH-RH** during prepubertal life, does not result from malfunction in the maturational processes in the germinal cells and the testes as a whole, despite the observation of changes in the testicular morphol. The **infertility** of LH-RH-A-treated male rats can be explained by the obsd. impairment of sexual behavior. A central action of the **antagonist** of **LHRH** when **administered** to immature male rats may thus lead to permanent changes in the development of sexual behavior.

L102 ANSWER 16 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 16
AN 113:17979 CA
TI A 90-day subcutaneous toxicity and fertility study of a LHRH antagonist in rats
AU Sundaram, Kalyan; Didolkar, Ashok K.; Keizer-Zucker, Anneke; DeJesus, William; Rivier, Jean; Vale, Wylie; Bardin, C. Wayne
CS Cent. Biomed. Res., Population Counc., New York, NY, 10021, USA
SO Fundam. Appl. Toxicol. (1990), 14(4), 734-44
CODEN: FAATDF; ISSN: 0272-0590
DT Journal

LA English
AB [Ac-D2Nal1,4Cl-DPhe2,D3Pal3,Arg5,DGlu6)anisole adduct),DAla10] **gonadotropin**-releasing hormone (Nal-Glu) is an **antagonist** of **LH-RH** and has the potential to be utilized as an antigonadal agent. A study was undertaken to evaluate the toxicol. effects of Nal-Glu in rats. Nal-Glu, dissolved in 5% mannitol in water contg. 9 mL/L benzyl alc., was **administered** s.c. In subchronic studies, groups of male and female rats received 0, 50, 250, or 1250 .mu.g/kg body wt. (BW) Nal-Glu for 90 days and were killed on day 91. Addnl. groups of male and female rats were given the high dose of Nal-Glu (1250 .mu.g/kg BW) or vehicle for either 30 or 90 days. Their **fertility** was assessed by mating them with normal animals. Unlike some other **LH-RH antagonists**, Nal-Glu exhibited a low potency for causing in vitro histamine release from rat peritoneal mast cells. Furthermore, in acute in vivo studies, Nal-Glu was less active in the induction of peripheral edema. In the subchronic study, all doses of Nal-Glu were well tolerated and there were no apparent systematic toxic effects. The pharmacol. effects of Nal-Glu were quite evident, however. Nal-Glu treatment led to a significantly decreased body wt. gain in the males and a significantly increased body wt. gain in the females. There was a dose-dependent decrease in wts. of gonads and **reproductive** organs in both the sexes. Some of the hematol. and serol. parameters were significantly different in Nal-Glu-treated animals. However, most of the values were within the normal range and are considered to be of no toxicol. significance. Histopathol. evaluations were made in the control and high-dose groups only. In the male, a seminiferous tubular degeneration and atrophy of the interstitial cells was seen. The prostate and seminal vesicles were also atrophied and the epididymides were devoid of spermatozoa. In the females, the **ovaries** and uteri were atrophic. The injection site of Nal-Glu-treated rats had inflammatory changes indicative of a local irritating action of the drug. All other tissues had normal histomorphol. Both male and female rats became **infertile** when 1250 .mu.g/kg Nal-Glu was **administered** for 30 days. Normal **fertility** was restored 8 wk after cessation of 90-day treatment. It is concluded that repeated **administration** of Nal-Glu leads to reversible **infertility** in both male and female rats. Although it was irritating at the site of injection, Nal-Glu had no systematic toxicol. effects.

L102 ANSWER 17 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 17
AN 113:185050 CA
TI Effects of a luteinizing hormone-releasing hormone antagonist in late-juvenile female rats: blockade of follicle growth and delay of first ovulation following suppression of gonadotropin concentrations
AU Meijs-Roelofs, H. M. A.; Kramer, P.; Van Cappellen, W. A.; Van Leeuwen, E. C. M.
CS Med. Fac., Erasmus Univ., Rotterdam, Neth.
SO Biol. Reprod. (1990), 43(4), 607-13
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB S.c. injections of an **antagonist** against **LH-releasing hormone** (LHRH-A, Org. 30276) were **administered** to late-juvenile female rats. The effects were studied on: timing of vaginal opening, 1st **ovulation**,

serum **gonadotropin** concns., and follicle growth. d. The dose of 100 .mu.g LHRH-A/100 g, given on days 28, 31, and 34, did not influence timing of 1st **ovulation**. After **administration** of 500 .mu.g LHRH-A/100 g, **ovulation** was retarded by 4.7 days if injections were given on days 28 and 31; by 6.7 days if given on days 28, 31, and 34; and by 11.5 days if given on days 28, 31, 34, and 37. Serum LH and FSH concns. 3 days after the 1st, 2nd, and 3rd injections of 500 .mu.g LHRH-A were lower than in saline-treated controls. **Ovarian** follicle counts showed decreased nos. of (antral) Class 2, 3, and 4 follicles 3 days after injection of 500 .mu.g LHRH-A/100 g on day 28, a higher no. of Class I follicles and a further decrease in Class 2, 3, and 4 follicles 3 days after the 2nd LHRH-A injection; and total absence of Class 3, 4, and 5 follicles 3 days after the 3rd LHRH-A injection. Six days after the 3rd LHRH-A injection, Class 2 and 4 follicles reappeared in the **ovaries**. A single, low-dose injection of LHRH-A **administered** at 0900 h on the day of 1st proestrus blocked 1st **ovulation** in 3 of 11 rats given 2.5 .mu.g and in all (8/8 and 12/12) rats given 5 and 10 .mu.g; **ovulation** was not blocked with 1 .mu.g LHRH-A (0/6 rats) or saline (0/8 rats). Thus, **administration** of LHRH-A to late-juvenile female rats may delay sexual maturation by a decrease in **gonadotropin** levels, causing arrest of follicle growth at an early antral stage. The dose of LHRH-A needed for acute inhibition of the 1st **ovulatory gonadotropin** surge is only a fraction of that causing chronically lower **gonadotropin** levels and subsequent blockade of follicle growth.

L102 ANSWER 18 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 18
AN 110:148164 CA
TI Immunoreactive inhibin concentrations in serum throughout the menstrual cycle of the macaque: suppression of inhibin during the luteal phase after treatment with an LH-RH antagonist
AU Fraser, H. M.; Robertson, D. M.; De Kretser, D. M.
CS MRC Reprod. Biol. Univ., Cent. Reprod. Biol., Edinburgh, EH3 9EW, UK
SO J. Endocrinol. (1989), 121(1), R9-R12
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB Concns. of immunoreactive inhibin in serum samples collected daily from adult stumptailed female macaques (Macaca artoides) during normal menstrual cycles were measured with a heterologous RIA. Serum inhibin concns. were low during the follicular phase of the cycle. After **ovulation** they began to rise, reaching a plateau at 8-11 days, before falling in parallel with the decline in luteal progesterone secretion. The dependence of the inhibin secretion by the corpus luteum on pituitary **gonadotropins** was investigated by the **administration** of an **LH-RH antagonist** [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Trp3,D-hArg(Et2)6,D-Ala10]LH-RH once daily for 3 days beginning on day 8 of the luteal phase. **LH-RH antagonist** treatment markedly suppressed serum levels of inhibin and progesterone and these remained at the level found in the follicular phase for the remainder of the luteal phase. Apparently, inhibin in the macaque is secreted into the peripheral blood almost exclusively during the luteal phase, being highest when FSH is at its nadir. Suppression of serum inhibin concns. during the luteal phase by **LH-RH antagonist** suggests that its secretion is integrated with the LH control of the corpus luteum.

L102 ANSWER 19 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 19
AN 112:16572 CA
TI Effects of LH-RH antagonist administration to immature male rats on sexual development
AU Van den Dungen, H. M.; Dijkstra, H.; Hiehle, M. A. H.; Van Rees, G. P.; Schoemaker, J.
CS Med. Fac., Univ. Leiden, Leiden, Neth.
SO Physiol. Behav. (1989), 46(5), 779-85
CODEN: PHBHA4; ISSN: 0031-9384
DT Journal
LA English
AB **Gonadotropin** secretion in immature male rats was inhibited by **administration** of a potent **LH-RH antagonist** (**LHRH**-A): from 6 to 15 days of age (early onset/short-term treatment), from 6 to 48 days of age (early onset/long-term treatment), or from 22 to 31 days of age (late onset/short-term treatment). Balano-preputial sepn. was retarded by 9 or 13 days (short-term treatments) or by .apprx.40 days (long-term treatment). Adult testicular wt. was lowered and plasma FSH was increased after early, but not after late onset of LHRH-A treatment. Plasma LH and testosterone levels were not affected by any of the LHRH-A treatments. **Fertility** was diminished after early onset LHRH-A **administration** only. Adult precopulatory and copulatory behavior were severly affected after early onset of LHRH-A treatment. Intensity of precopulatory anogenital inspection was increased. The copulatory pattern was incomplete with absence of ejaculatory behavior during sexual behavior tests. Sexual behavior was not affected after late onset of LHRH-A treatment. Thus, **administration** of LHRH-A to immature male rats delays balano-preputial sepn. irresp. of the age of onset of LHRH-A treatment. In contrast, the effects on adult FSH levels, testicular wt., **fertility**, and sexual behavior depend on age and duration of LHRH-A **administration**.

L102 ANSWER 20 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 20
AN 111:209413 CA
TI Diminished role of LH-RH in the control of gonadotroph morphology and function in the long-term castrated male rat
AU Almeida, O. F. X.; Hassan, A. H. S.; Nikolarakis, K. E.; Martin, G. B.
CS Inst. Pharmacol. Toxicol. Pharm., Ludwig-Maximilians-Univ., Munich, D-8000/22, Fed. Rep. Ger.
SO J. Endocrinol. (1989), 123(2), 263-73, 1 plate
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB Previous studies showed that the neurotransmitter control of the secretion of LH-RH and LH differs between long-term castrated and **ovariectomized** rats. Thus, it was examd. how **gonadotrophs** of long-term castrated rats maintain a high level of LH secretion. Evidence for a reduced dependence of the **gonadotrophs** upon LH-RH stimulation is provided. Although sensitivity to native LH-RH was not completely lost in long-term castrated rats, 2 potent **LH-RH antagonists** (D-pyroglu1,D-Phe2,D-Trp3,6)-LH-RH and (N-acetyl-3,4-dehydro-Pro,p-fluoro-D-Phe2,D-Trp3,6)-LH-RH, inhibited LH secretion in short-term castrated and long-term **ovariectomized** rats, but not in long-term castrated rats. Neither blockade of axonal transport with colchicine nor

immunoneutralization of LH-RH with an antiserum against LH-RH (both **administered** 48 h before blood sampling) produced redns. in serum concns. of LH in long-term castrated rats, although these treatments suppressed LH levels in short-term castrated animals. Chronic (6-day) infusions of the 2nd **LH-RH antagonist** (up to 450 .mu.g/day) neither reduced LH secretion nor altered the morphol. of the castration cells in the pituitaries of long-term castrated rats. Chronic treatment with testosterone (15 days), however, reversed these parameters to some extent, and when the testosterone treatment was coupled with chronic infusions of the **LH-RH antagonist**, lower serum levels of LH and redns. in the size of the castration cells were obsd. Thus, castration cells may function autonomously, without the need for LH-RH, and testosterone in some way restores the dependency on LH-RH and(or) the responsiveness to LH-RH of these cells.

L102 ANSWER 21 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 21
AN 107:127532 CA
TI Suppression of luteal function by a luteinizing hormone-releasing hormone antagonist during the early luteal phase in the stumptailed macaque monkey and the effects of subsequent administration of human chorionic gonadotropin
AU Fraser, Hamish M.; Nestor, John J., Jr.; Vickery, Brian H.
CS MRC Reprod. Biol. Unit, Cent. Reprod. Biol., Edinburgh, EH3 9EW, UK
SO Endocrinology (Baltimore) (1987), 121(2), 612-18
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
AB To investigate whether a prolonged suppression of LH release during the early luteal phase could result in a sustained suppression of progesterone, 10 monkeys (Macaca arctoides) were treated with 3 consecutive daily injections of 300 .mu.g **LH-RH antagonist**/kg beginning on days 0, 1, 2, 3, 4, and 5 after the LH surge. When the antagonist was **administered** on the day of the LH surge, serum concns. of bioactive LH were still elevated on the following day, but then fell to low levels. Serum progesterone concns. were subnormal in these monkeys for the next 10 days, but recovered toward the late luteal phase. In monkeys receiving antagonist starting on days 1-5 after the LH surge, serum concns. of bioactive LH were suppressed to near the detection limit of the assay for 4 days after the first injection. Seven of the 8 monkeys demonstrated a progressive decline in serum progesterone concns. to undetectable values which remained for the duration of the luteal phase. In the remaining monkey the decline in progesterone was less marked; this animal presented a normal progesterone profile 3 days after the last antagonist injection. Premature menses occurred in all 8 monkeys; the next **ovulation** occurred 18.9 days after the last antagonist injection. To test luteal function after antagonist treatment during the early luteal phase and to mimic the rescue of the corpus luteum during a **fertile** cycle and assess the contraceptive effects of antagonists, human chronic **gonadotropin** (hCG) in daily doses of 30, 60, 90, 180, and 360 IU was **administered** starting on day 7 of the luteal phase to monkeys previously treated with 3 daily injections of 300 .mu.g antagonist/kg during the early luteal phase. In controls, hCG **administration** elevated serum progesterone concns. to 15-20 ng/mL. In 3 monkeys in which antagonist **administration** did not commence until day 5 or 6, hCG overcame the suppressive

effect of the antagonist. However, in 7 monkeys in which antagonist **administration** began on days 1-4, hCG caused only a small progesterone rise (maximal range, 1.8-4.9 ng/mL), .apprx.20% of that obsd. in control monkeys receiving hCG. Thus, the macaque corpus luteum is dependent upon **gonadotropin** support during the early luteal phase. Recovery of pituitary function after 3-day **LH-RH antagonist administration** fails to restore luteal progesterone secretion, and the ability of subsequent **administration** of hCG to rescue the corpus luteum is impaired.

L102 ANSWER 22 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 22
AN 106:113706 CA
TI Inhibition of first ovulation: administration of an LH-RH antagonist to immature female rats
AU Meijs-Roelofs, H. M. A.; Kramer, P.; Van Cappellen, W. A.; Schuiling, G. A.
CS Med. Fac., Erasmus Univ., Rotterdam, 3000 DR, Neth.
SO J. Endocrinol. (1987), 112(3), 407-15
CODEN: JOENAK; ISSN: 0022-0795
DT Journal
LA English
AB The **LH-RH antagonist** Org. 30093 (I) [78493-58-0] as a single high dose (50 .mu.g, s.c.) or as repeated daily doses of 5-30 .mu.g I/day, **administered** to immature female rats between 28 and 38 days of age, had no effect on the age or body wt. at the time of vaginal opening or the 1st **ovulation**. If repeated daily doses of 2 .times. 10 .mu.g I were given from 32 to 42 or from 37 to 47 days of age, 1st **ovulation** was delayed by 3.0 and 6.3 days, resp. **Administration** of 10 .mu.g I at 09.00 h and again at 17.00 h on the day of 1st proestrus was sufficient to block the expected 1st **ovulation** in 36 of 38 rats. This effect could be repeated by **administering** the same doses of I at proestrus and again on the next day: **ovulation** was blocked in 8 of 8 rats. A single dose of I (10 .mu.g) **administered** on the morning of proestrus blocked **ovulation** in 5 of 12 rats. Both the preovulatory LH [9002-67-9] and FSH [9002-68-0] surge, as measured at 16.00 h on proestrus, were inhibited by I treatment. On the day after proestrus no recruitment of new small antral follicles occurred in rats with **ovulatory** blockade. Delayed **ovulation** took place 2-5 days after I injection at proestrus: until 3 days after injection rats were able to **ovulate** their original preovulatory follicles, thereafter newly developed follicles **ovulated** and large **ovarian** cysts were found in the **ovaries**, next to fresh corpora lutea. Chronic **administration** of 2 injections daily of 10 .mu.g I from 34 days of age until the morning of 1st proestrus had only marginal effects on the timing of 1st proestrus and on follicle dynamics. Thus, in chronic as well as in acute expts., 1st **ovulation** could only be delayed by I **administration** on the day of 1st proestrus and the effect was due to acute inhibition of the preovulatory **gonadotropin** surge.

L102 ANSWER 23 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 23
AN 106:96351 CA
TI Suppression of spermatogenesis in a nonhuman primate (Macaca fascicularis) by concomitant gonadotropin-releasing hormone antagonist and testosterone treatment

AU Weinbauer, G. F.; Surmann, F. J.; Nieschlag, Eberhard
CS Dep. Exp. Endocrinol., Univ. Women's Hosp., Muenster, D-4400, Fed. Rep. Ger.
SO Acta Endocrinol. (Copenhagen) (1987), 114(1), 138-46
CODEN: ACENA7; ISSN: 0001-5598
DT Journal
LA English
AB The effects of concomitant testosterone (T) [58-22-0] supplementation on **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] **antagonist**-induced testicular regression in cynomolgus monkeys (M. fascicularis) were investigated. Four adult monkeys were infused via osmotic minipumps with daily amts. of 2 mg of a potent GnRH antagonist, RS-68439 [89662-30-6], for a period of 104 days. Androgen substitution was provided via T-filled silastic capsules implanted at initiation of GnRH antagonist treatment. Within 1-4 days of GnRH antagonist **administration**, serum concns. of bioactive LH [9002-67-9] became undetectable. The implants maintained serum T at 50-80% of pretreatment levels. Sperm prodn. decreased in 3 out of 4 monkeys. One animal became azoospermic by the 13th week of treatment, and the ejaculates of 2 other monkeys contained <5 .times. 106 sperm. Testicular histol., judging from biopsies at termination of GnRH antagonist treatment, was typical of the hypogonadotropic status in 3 of the 4 monkeys. The most affected tubules contained only spermatogonia and Sertoli cells. Although comparison with GnRH antagonist treatment alone in a previous study indicated a delay of spermatogenic inhibition with testosterone, the potential of GnRH antagonist for male **fertility** regulation was confirmed.

L102 ANSWER 24 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 24
AN 109:67208 CA
TI Neonatal treatment with a LH-RH-antagonist: effects on pubertal development in female and male rats
AU Van den Dungen, H. M.; Van Rees, G. P.; Meijs-Roelofs, H. M. A.; Kramer, P.; Tilders, F. J. H.; Schoemaker, J.
CS Dep. Gynecol. Obstet., Vrije Univ., Amsterdam, Neth.
SO Int. Congr. Ser. - Excerpta Med. (1987), 751(Neuro-Endocrinol. Reprod.), 75-84
CODEN: EXMDA4; ISSN: 0531-5131
DT Journal
LA English
AB To establish the importance of early **gonadotropin** secretion in vivo for the normal development of puberty, this development was studied in male and female rats that had been chronically treated with an **antagonist** to **LH-RH** (ORG. 30276). **Administration** of the **LH-RH antagonist** resulted in a chronic significant suppression of the plasma FSH levels on days 6-21 in the female and up to day 18 in the male rat. The LH levels in the treated female and male rats were suppressed significantly up to about day 18 and from then on remained in the control range until day 120. From day 24 on the plasma FSH levels of the females in the antagonist-treated and control group did not differ at any age to day 120. In the control male rat the normal prepubertal FSH rise was seen from 24 days of age onwards. The antagonist-treated males, however, showed a significantly steeper elevation from day 24 onwards that progressed gradually to about twice the control levels on day 35. These high FSH levels persisted into adulthood (120 days of age), when they were still elevated by .apprx.50%. The wt. of the uteri and **ovaries** were reduced in the treated group and the

vaginal opening developed abnormally. The wts. of testes from the **LH-RH antagonist**-treated group were significantly lower than controls. The tubular diam. in the testis was also significantly reduced by ORG. 30276. Whether the effects on pubertal development of treatment of neonatal rats with ORG. 30276 are mediated by the suppression of FSH and(or) LH, or by a direct effect on the gonads, or even via LH-RH itself needs to be further investigated.

L102 ANSWER 25 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 25
AN 105:36003 CA
TI Different neuroendocrine mechanisms regulate the acute pituitary follicle-stimulating hormone response to orchidectomy and ovariectomy
AU Berardo, Peter V.; DePaolo, Louis V.
CS Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA
SO Neuroendocrinology (1986), 43(4), 511-18
CODEN: NUNDAJ; ISSN: 0028-3835
DT Journal
LA English
AB Expts. were conducted to det. whether a sex difference exists in neuroendocrine mechanisms controlling acute pituitary FSH [9002-68-0] responses to castration. Adult male rats and 4-day cycling female rats on diestrus 1 were injected i.p. with either phenobarbital Na (PhB) [57-30-7] (80 mg/kg) or vehicle at 08.00 h. Following a blood collection at 10.00 h, rats given PhB or vehicle were either sham castrated or castrated under ether. Addnl. blood samples were obtained, and supplemental PhB or vehicle injections were given at 3, 8, 13, 18, and 24 h after castration. **Administration** of PhB to male rats completely prevented acute increases in plasma LH [9002-67-9] and FSH levels after orchidectomy (ORDX). In contrast, PhB treatment did not prevent initial rises in plasma FSH levels at 8 h after **ovariectomy** (OVX) and only partially suppressed OVX-induced increases in plasma FSH levels between 13 and 24 h. Plasma LH levels were not elevated by 24 h after OVX. To specifically evaluate the role of LH-RH [9034-40-6] in mediating the PhB-sensitive rises in **gonadotropins** after castration, groups of male rats and female rats at estrus were injected s.c. with 400 .mu.g of a potent **LH-RH antagonist**, [Ac-.DELTA.3-Pro1,pF-D-Phe2,D-Trp3,6]LH-RH (ALHRH) [78708-43-7], or oil at 12.00 h. At 10.00 h on the next morning, an initial blood sample was taken, and all rats were castrated under ether. Addnl. blood samples were taken at times indicated in the previous expt. Similar to PhB, ALHRH completely abolished ORDX-induced increases in circulating LH and FSH levels. In contrast to PhB, ALHRH partially suppressed increases in plasma FSH levels 8 h after OVX. Similar to PhB, however, ALHRH partially suppressed FSH levels between 13 and 24 h. In a final expt., FSH release was episodic 20-24 h after either ORDX or OVX, but not 8-12 h after OVX. Taken together, these results clearly demonstrate that acute increases in nonepisodic FSH secretion after ORDX are totally mediated by LH-RH. In contrast, acute increases in the nonepisodic component of FSH secretion after OVX are due to both an LH-RH-dependent and LH-RH-independent mechanism (i.e., increase in basal FSH secretion). Finally, in view of the LH-RH-independent control of pulsatile FSH release, the present results suggest that central mechanisms regulating episodic discharges of FSH become activated between 13 and 24 h after OVX.

L102 ANSWER 26 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 26

AN 104:162174 CA
TI Inhibition of estradiol-induced gonadotropin release in ovariectomized rhesus macaques by a gonadotropin-releasing hormone antagonist
AU Norman, Reid L.; Rivier, Jean; Vale, Wylie; Spies, Harold G.
CS Health Sci. Cent., Texas Tech Univ., Lubbock, TX, 79430, USA
SO Fertil. Steril. (1986), 45(2), 288-91
CODEN: FESTAS; ISSN: 0015-0282
DT Journal
LA English
AB Adult **ovariectomized** rhesus macaques were given the **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] **antagonist** [Ac-.beta.-(2)-D-naphthalenyl-D-Ala1, p-fluoro-D-Phe2,D-Trp3,D-Arg6]-GnRH, by i.v. infusion for 3-3.5 days to det. whether the pos. feedback action of estradiol (E2) [50-28-2] on pituitary LH [9002-67-9] secretion could be inhibited by blockage of GnRH binding to pituitary **gonadotropes**. The LH release was suppressed when the antagonist was given either as a bolus injection every 6 h or as a const. infusion, beginning 24 h after the E2 was **administered**. Both LH release and FSH [9002-68-0] release were suppressed if the GnRH antagonist infusion began when the E2 was **administered**. Thus continued hypothalamic GnRH stimulation of the pituitary is necessary for the full expression of the preovulatory-like **gonadotropin** surge that occurs in **ovariectomized** macaques in response to E2.

L102 ANSWER 27 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 27
AN 104:219512 CA
TI The role of catecholamines in the regulation of an induced wave of gonadotropins in ovariectomized rats
AU Bukiya, N. G.; Babichev, V. N.; Adamskaya, E. I.
CS Lab. Fiziol. Endokrin. Sist., Inst. Eksp. Endokrinol. Klrim. Gormon., Moscow, USSR
SO Probl. Endokrinol. (1986), 32(2), 47-51
CODEN: PROEAS; ISSN: 0375-9660
DT Journal
LA Russian
AB The effects of various catecholamine agonists and **antagonists** on **LH-RH** [**9034-40-6**] levels in the preoptic area, arcuate nucleus, and median eminence and on induced surges of FSH [9002-68-0] and LH [9002-67-9] secretion were studied in **ovariectomized** rats. .alpha.-Adrenergic blockade (phentolamine or prazosin) inhibited induced **gonadotropin** release. The **gonadotropin** surge response was recovered when the .alpha.-adrenergic agonist mesaton was **administered** to previously blocked animals. Dopaminergic agonists (apomorphine) had no effect on the **gonadotropin** surge in adrenoceptor blocked rats. Changes in hypothalamic LH-RH levels during the **gonadotropin** surge and during its blockade and restoration by pharmacol. agents indicated that catecholamines were involved in both the metabolic processes and transport of this neuropeptide. Thus, central catecholaminergic regulation of the **gonadotropin** surge is due primarily to its effect on hypothalamic LH-RH.

L102 ANSWER 28 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 28
AN 103:154494 CA
TI Effect of an antagonistic analog of LH-RH on haloperidol-induced hyperprolactinemia in female rats

AU Debeljuk, L.; Torres-Aleman, I.; Schally, A. V.
CS Endocr. Polypept. Lab., VA Med. Cent., New Orleans, LA, 70146, USA
SO Peptides (Fayetteville, N. Y.) (1985), 6(3), 463-5
CODEN: PPTDD5; ISSN: 0196-9781
DT Journal
LA English
AB The effects of prolonged treatment with the **antagonistic** analog of **LH-RH** (ORG 30276 [83539-08-6]) on the hyperprolactinemia induced by haloperidol were investigated in intact or **ovariectomized** female rats. Treatment with ORG 30276 for 20 days reduced prolactin [9002-62-4] levels elevated by daily injections of haloperidol in intact as well as in **ovariectomized** rats. **Administration** of ORG 30276 also decreased serum LH [9002-67-9] levels in both types of rats. Thus, the **LH-RH antagonist** is able to counteract the hyperprolactinemic effect of haloperidol. This effect might be due to a blockade of the action of endogenous LH-RH on the **gonadotrophs** resulting in a suppression of the paracrine action of these cells on the lactotroph.

L102 ANSWER 29 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 29
AN 100:151175 CA
TI Counteractive effects of agonistic and antagonistic gonadotropin-releasing hormone analogs on spermatogenesis: sites of action
AU Heber, David; Dodson, Robin; Peterson, Margaret; Channabasavaiah, K. C.; Stewart, John M.; Swerdloff, Ronald S.
CS Dep. Med., Harbor-UCLA Med. Cent., Torrance, CA, 90509, USA
SO Fertil. Steril. (1984), 41(2), 309-13
CODEN: FESTAS; ISSN: 0015-0282
DT Journal
LA English
AB Both **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] agonistic and **antagonistic** analogs inhibit **reproductive** hormonal function, but neither class of analog completely inhibited spermatogenesis in man. The potential for a synergistic interaction of submaximal doses of these 2 classes of GnRH analogs was investigated by daily s.c. injections of 200 ng/day of a potent agonist (D-Leu6des-Gly10-GnRH ethylamide [53714-56-0]) and 100 .mu.g/day of a potent antagonist (NAc-L-Ala1,pCl-D-Phe2,D-Trp3,6-GnRH [81557-54-2]), both alone and in combination, to adult male rats for 21 days. Serum **gonadotropins** and testosterone, pituitary GnRH receptor content, gonadal **gonadotropin** receptors, and intratesticular sperm counts were quantitated in each treatment group. Despite the ability of both GnRH agonists and antagonists to inhibit **reproductive** function when **administered** as single agents, combined treatment with the 2 classes of GnRH analogs was less effective than either agent alone at these doses in the pharmacol. suppression of spermatogenesis.

L102 ANSWER 30 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 30
AN 101:222877 CA
TI Biological activity of a highly potent LH-RH antagonist
AU McRae, Georgia I.; Vickery, Brian H.; Nestor, John J., Jr.; Bremner, William J.; Badger, Thomas M.
CS Dep. Physiol., Inst. Biol. Sci., Palo Alto, CA, 94304, USA
SO LHRH Its Analogs (1984), 137-51. Editor(s): Vickery, Brian H.; Nestor, John J., Jr.; Hafez, E. S. E. Publisher: MTP, Lancaster, UK.
CODEN: 52RGAC

DT Conference
LA English
AB The biol. activities of RS-29226 (I) [82778-58-3] were examd. in a variety of test systems. I (1.0-16.0 .mu.g) dose-dependently inhibited **ovulation** in rats when **administered** s.c. at noon on the day of diestrus. The propylene glycol/saline vehicle was more efficient than the corn oil vehicle. The requirement for I increased when it was **administered** earlier in the cycle. **Ovulation** was also inhibited by 2 analogs of I and the relative activities were discussed in relation to structure. Continuous superfusion of a pituitary culture system with I (20 ng/mL) inhibited the release of LH [9002-67-9] in response to LH-RH (20 ng/mL). I (500 .mu.g/kg, s.c.) also suppressed LH in castrated rats but had a lesser effect on FSH [9002-68-0] levels. I (80 .mu.g/rat/day) for 14 days abolished the **ovarian** cycle in rats and lower levels resulted in continuous estrus or diestrus. I (200 .mu.g/rat) terminated pregnancy when **administered** on the 10th day. I (1 mg/rat/day, s.c.) for 14 days decreased plasma testosterone [58-22-0] and suppressed **reproductive** organ wt. and spermatogenesis. A single injection of I (100 or 1000 mg/kg, s.c.) also suppressed plasma testosterone and **gonadotropins** in dogs and 5 mg I/kg, s.c. to a male cynomolgus monkey suppressed plasma testosterone for >24 h. The applicability of **LH-RH antagonist** analogs are briefly discussed in relation to their increased binding affinities and the rapidity and longevity of their suppressive effects on the pituitary and therefore, gonadal function.

L102 ANSWER 31 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 31
AN 99:188151 CA
TI Comparison of the effect of several gonadotropin releasing hormone antagonists on luteinizing hormone secretion, receptor binding and ovulation
AU Rivier, Catherine; Rivier, Jean; Perrin, Marilyn; Vale, Wylie
CS Salk Inst., San Diego, CA, 92031, USA
SO Biol. Reprod. (1983), 29(2), 374-8
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB Acetyl dehydro3,4-Pro1,p-fluoro-D-Phe2,D-Trp3,6]-LH-RH (I) [78708-43-7], acetyl dehydro3,4-Pro1,p-fluoro-D-Phe2,.beta.-naphtyl-2-D-Ala3,6]-LH-RH [87687-21-6], and acetyl .beta.-naphtyl-2-D-Ala1,p-fluoro-D-Phe2,D-Trp3,D-Arg6]-LH-RH (II) [87687-22-7] were highly effective in suppressing LH [9002-67-9] secretion in cultured rat anterior pituitary cells, whereas I was the most effective in preventing the binding of a radiolabeled ligand to receptors of these cells. II, given intragastrically, was the most effective in inhibiting LH secretion in **ovariectomized** rats and to block **ovulation** in intact rats. Although <1% of the intragastric dose of these LH-RH analogs is absorbed, the intragastric **administration** of **LH-RH antagonists** can decrease **gonadotropin** secretion and interfere with **reproductive** function.

L102 ANSWER 32 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 32
AN 96:98038 CA
TI Diurnal influences on serum luteinizing hormone responses to opiate receptor blockade with naloxone or to luteinizing hormone-releasing hormone in the immature female rat

AU Blank, Michael S.; Mann, David R.
CS Yerkes Reg. Primate Res. Cent., Emory Univ., Atlanta, GA, 30322, USA
SO Proc. Soc. Exp. Biol. Med. (1981), 168(3), 338-43
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English
AB The existence of a temporal pattern in the **gonadotropin** response of immature rats to LH-RH [**9034-40-6**] or the opiate **antagonist**, naloxone [465-65-6], was investigated. The serum LH [9002-67-9] response to naloxone and LH-RH varied with the time of day. Naloxone **administration** had no effect on levels of serum LH at 1500 and 1800 h, but induced a rise in serum LH at all other times. Naloxone had its greatest effect during the late evening and early morning hours. A similar, but not identical, pattern of LH responsiveness to LH-RH was obsd., with the 2 rhythms being truly divergent only during the late afternoon when LH sensitivity was high to LH-RH but low to naloxone. Evidently, there is a diurnal pattern of pituitary sensitivity to both naloxone and LH-RH in the immature rat; for the most part, temporal variations in the LH response to opiate antagonists result from altered pituitary sensitivity to endogenous LH-RH. However, the enhanced response of the pituitary to LH-RH in the late afternoon, when opioid inhibition of hypothalamic LH-RH secretion is at a nadir could provide a mechanism in the immature rat whereby adult-like LH surges can be stimulated. The early afternoon LH response to various doses of naloxone was examd. in intact and **ovariectomized** 30-day-old rats. Intacts displayed a lower abs. but higher percentage increase above basal values of LH than did **ovariectomized** animals. These findings contrast with those previously found in adult female rats.

L102 ANSWER 33 OF 33 CA COPYRIGHT 1997 ACS DUPLICATE 33
AN 94:41804 CA
TI Inhibition of preovulatory gonadotropin secretion in the rhesus monkey by [(<Glu-Pro)1,D-Phe2,D-Trp3,6]-LHRH
AU Wilks, John W.; Folkers, Karl; Bowers, Cyril Y.; Humphries, John; Schircks, Bernhard; Friebel, Klaus
CS Upjohn Co., Kalamazoo, MI, 49001, USA
SO Contraception (1980), 22(3), 313-23
CODEN: CCPTAY; ISSN: 0010-7824
DT Journal
LA English
AB [(Pyro-Glu-Pro)1, D-Phe2, D-Trp3,6]-LH-RH [69770-59-8] was **administered** to a rhesus monkey beginning on Day 9 of the menstrual cycle; **ovulation** did not occur and preovulatory peaks of LH [9002-67-9] and FSH [9002-68-0] were not obsd. despite elevations in serum estradiol [50-28-2] of sufficient strength and duration to elicit **gonadotropin** surges. Midcycle **gonadotropin** surges had already commenced in another monkey, however the antagonist did partially inhibit LH and FSH secretion although **ovulation** and luteinization were not prevented. Normal hormone secretion patterns and luteal function were obsd. in another monkey when the antagonist was given after the midcycle FSH and LH peaks had already occurred. These data emphasize the importance of beginning treatment with **LH-RH antagonists** early in the follicular phase of the menstrual cycle.

=> fil
biosi,medl,embas,lifesci,biotechd,wpid,confsci,dissabs,scisearch,jicst,promt,toxlit,toxlin
Searcher : Shears 308-4994

FILE 'BIOSIS' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'MEDLINE' ENTERED AT 16:53:56 ON 03 SEP 1997

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FILE 'DISSABS' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'SCISEARCH' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'JICST-EPLUS' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'PROMT' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'TOXLIT' ENTERED AT 16:53:56 ON 03 SEP 1997

FILE 'TOXLINE' ENTERED AT 16:53:56 ON 03 SEP 1997

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=> s l98
L103        27 FILE BIOSIS
L104        25 FILE MEDLINE
L105        31 FILE EMBASE
'CN' IS NOT A VALID FIELD CODE
L106         4 FILE LIFESCI
L107         0 FILE BIOTECHDS
'CN' IS NOT A VALID FIELD CODE
L108         3 FILE WPIDS
'CN' IS NOT A VALID FIELD CODE
L109         0 FILE CONFSCI
'CN' IS NOT A VALID FIELD CODE
L110         1 FILE DISSABS
'CN' IS NOT A VALID FIELD CODE
L111        15 FILE SCISEARCH
L112         0 FILE JICST-EPLUS
L113         0 FILE PROMT
L114        32 FILE TOXLIT
L115         6 FILE TOXLINE

TOTAL FOR ALL FILES
L116       144 L98
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=> s l116 not l45
L117        23 FILE BIOSIS
L118        20 FILE MEDLINE
L119        26 FILE EMBASE
L120         4 FILE LIFESCI
L121         0 FILE BIOTECHDS
L122         3 FILE WPIDS
L123         0 FILE CONFSCI
L124         1 FILE DISSABS
L125        11 FILE SCISEARCH
L126         0 FILE JICST-EPLUS
L127         0 FILE PROMT
L128        29 FILE TOXLIT
L129         5 FILE TOXLINE

TOTAL FOR ALL FILES
L130       122 L116 NOT L45

=> dup rem l130
PROCESSING COMPLETED FOR L130
L131        47 DUP REM L130 (75 DUPLICATES REMOVED)

=> s l130 and (treat? or therap? or control? or regulat?)
=> d l131 1-47 bib abs; fil uspat; s  l98

L131 ANSWER 1 OF 47  BIOSIS  COPYRIGHT 1997 BIOSIS     DUPLICATE 1
AN  97:351910  BIOSIS
DN  99651113
TI  Effects of progesterone on the secondary surge of
    follicle-stimulating hormone in the rat.
AU  Tebar M; Uilenbroek J T J; Kramer P; Van Schaik R H N; Wierlikx C D
    J; Ruiz A; De Jong F H; Sanchez-Criado J E
CS  Dep. Physiol., Fac. Med., Univ. Cordoba, Avda. Menendez Pidal s/n,
    14004 Cordoba, Spain
SO  Biology of Reproduction 57 (1). 1997.  77-84. ISSN: 0006-3363
LA  English
AB  In the cyclic rat, the secondary surge of FSH on estrus appears to
    depend on the LH surge-induced fall in serum concentrations of
    inhibin. To investigate the involvement of progesterone in the
    regulation of the secondary surge of FSH, 4-day cyclic rats were
    treated on proestrus with an antagonist of LHRH
    (LHRHant) and with an ovulatory dose of ovine (o) LH,
    progesterone, the antiprogestin RU486, or the combination of RU486
    and oLH. Serum concentrations of gonadotropins and inhibin
    at 1830 h on proestrus and at 0030 h on estrus were determined, and
    the expression of inhibin/activin subunit mRNAs in the ovary
    at 0030 h on estrus was analyzed by in situ hybridization. Rats
    receiving saline showed low expression of alpha-, beta-A-, and
    beta-B-subunit mRNAs in the ovary and low serum levels of
    inhibin in conjunction with the elevated serum concentrations of FSH
    on estrus. Administration of LHRHant blocked the decrease
    in the synthesis and secretion of inhibin and abolished the FSH
    secondary surge, whereas the injection of oLH prevented these
    effects. Exogenous progesterone, compared with LHRHant injection,
    increased alpha-, beta-A-, and beta-B-subunit mRNA hybridization
    intensity in the ovary and serum inhibin immunoreactivity,
    and also restored, in part, the surge of FSH on estrus. The
    antiprogestin RU486 did not modify the effect of oLH on either
    inhibin/activin subunit mRNAs in the ovary or serum levels
    of inhibin, but blocked the FSH surge. These results indicate that,
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in the cyclic rat, 1) the secretion of progesterone on proestrous afternoon, induced by the LH surge, is not involved in the fall of **ovarian** inhibin synthesis and secretion; and 2) in combination with a drop in serum inhibin, a stimulatory action of progesterone on another factor, possibly pituitary activin, could be necessary to elicit a complete secondary surge of FSH.

L131 ANSWER 2 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 2
AN 96:410782 BIOSIS
DN 99133138
TI Recombinant FSH-induced follicle development in immature rats treated with an LHRH antagonist: A direct effect of RU486 on follicular atresia.
AU Uilenbroek J T J; Kramer P; Van Leeuwen E C M; Karels B; Timmerman M A; De Jong F H; De Leeuw R
CS Dep. Endocrinol. Reproduction, Fac. Med. Health Sci., Erasmus Univ. Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands
SO Journal of Endocrinology 150 (1). 1996. 85-92. ISSN: 0022-0795
LA English
AB To investigate whether the progesterone antagonist RU486 has a direct effect on **ovarian** function, it was **administered** to immature female rats rendered hypogonadotrophic by **administration** of an **LHRH antagonist** and in which follicle development was stimulated by recombinant human FSH (recFSH). In the first experiments the effects of **LHRH antagonist** and recFSH on follicle growth were evaluated. Female rats of 22 days of age were injected with an LHPH antagonist (Org 30276; 500 mu-g/100 g body weight) every other day. This treatment resulted in a tenfold decrease in serum LH concentrations and a twofold decrease in serum FSH concentrations at day 30 and caused a reduction in the number and size of antral follicles. Treatment with recFSH (Org 32489) twice daily from day 26 for 4 days in a total dose ranging from 5 to 20 IU/animal increased the number and size of antral follicles in a dose-related manner and resulted after 20 IU recFSH in a tenfold increase in the concentration of inhibin in serum and **ovaries** at day 30. Once it was established that **LHRH antagonist** treatment in immature rats could be used to study the effects of **gonadotrophins** or steroids on follicle function, this animal model was used to study the effects of RU486 on the **ovary**. RU486 was **administered** (twice daily for 4 days, 1 mg/injection) to **LHRH antagonist**-treated rats in which follicular growth and differentiation were stimulated by 10 IU recFSH or by 10 IU recFSH plus 0.5 IU human chorionic **gonadotrophin** (hCG). RU486 had no effect on circulating levels of LH and FSH, but stimulated follicular atresia both in rats treated with recFSH alone and in rats treated with recFSH and hCG. Inhibin concentrations both in serum and **ovaries** were significantly increased after hCG treatment. RU486, however, did not increase inhibin in the rats treated with recFSH and in those treated with recFSH and hCG. In summary, the present study has demonstrated that (1) immature rats treated with an **LHRH antagonist** can be used to study the effects of **gonadotrophins** and steroids on follicular function and (2) RU486 has a direct stimulatory effect on follicular atresia.

L131 ANSWER 3 OF 47 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-090680 [12] WPIDS
CR 95-147146 [12]
DNC C95-041027

TI New N-terminal acylated deca- and undeca peptide cpds. - useful as potent antagonists of LHRH, e.g. for treating benign prostatic hyperplasia, tumours, hirsutism, gastric motility disorders, etc..
DC B04
IN FITZPATRICK, T D; HAVIV, F; MORT, N A; NICHOLS, C J; SWENSON, R E
PA (TAPP-N) TAP PHARM INC; (TAPH-N) TAP HOLDINGS INC; (ABBO) ABBOTT LAB
CYC 20
PI WO 9504541 A1 950216 (9512)* EN 92 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP
US 5413990 A 950509 (9524) 12 pp
US 5502035 A 960326 (9618) 33 pp
EP 738154 A1 961023 (9647) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
JP 09501913 W 970225 (9718) 148 pp
ADT WO 9504541 A1 WO 94-US8678 940729; US 5413990 A US 93-103022 930806; US 5502035 A CIP of US 93-103474 930806, US 94-279677 940727; EP 738154 A1 EP 94-924100 940729, WO 94-US8678 940729; JP 09501913 W WO 94-US8678 940729, JP 95-506473 940729
FDT EP 738154 A1 Based on WO 9504541; JP 09501913 W Based on WO 9504541
PRAI US 94-279677 940727; US 93-103022 930806; US 93-103474 930806
AN 95-090680 [12] WPIDS
CR 95-147146 [12]
AB WO 9504541 A UPAB: 950530
Peptides of formula X-A-B-C-D-E-F-G-H-I-J-K (I) and their salts are new. In the formula, X= an acyl gp. chosen from dihydroshikimyl, 2- or 3-furoyl, tetrahydrofur-2- or 3-yl, (thien-2- or 3-yl)carbonyl, (tetrahydrothien-2- or 3-yl)carbonyl, (pyrrol-2- or 3-yl)carbonyl, Pro, N-acetyl-prolyl, 3-(indolin-3-yl)propionyl, etc.; A = absent or is D-Ala, 3-aminopropionyl, 4-aminobutyryl, 5-aminovaleryl, 6-amino-hexanoyl, 8-aminooctanoyl, 7-amino-heptanoyl, 11-aminoundecanoyl, azaglycyl, Gly, sarcosyl or D-Ser; B = D-Phe, D-3-(4-chloro- or -fluoro-phenyl)alanyl, D-3-(quinolin-3-yl)alanyl, sarcosyl, Gly, azaglycyl, D-3,3-diphenylalanyl, N-alpha-methyl-D-3-(naphth-2-yl)alanyl or D-3-(naphth-2-yl)alanyl; C = D-3-(4-chloro- or -fluoro-phenyl)alanyl, D-3,3-diphenylalanyl, D-3-(naphth-2-yl)alanyl, D-phenylalanyl or D-3-(quinolin-3-yl)alanyl; D = D-Ala, D-3-W-alanine or Gly; W = benzo[b]thien-2-yl, naphth-1-yl, pyrid-3-yl, quinolin-3-yl or thiazol-2-yl; E = Gly, L-Ser, L-homoseryl, L-seryl(O-benzyl) or N-alpha-(R1)-L-seryl; R1 = 1-4C alkyl; F = N-alpha-(R'')-Ala, N-alpha-(R'')-(3-(4-(3-amino-1,2,4-triazol-5-yl) amino) phenyl)alanyl, N-alpha-(R'')-(3-(4-((3-amino- 1,2,4-triazol- 5-amino) methyl) phenyl)alanyl, N-alpha-(R'')-(3-(4-(3-amino- 1,2,4-triazol-5-yl) amino) cyclohexyl) alanyl, N-alpha-(R'')-(3-(4-(nicotinyl)amino) cyclohexyl) alanyl, N-alpha-(R'')-(N-epsilon-nicotinyl) lysyl, etc.; G = Gly, D-citrullyl, D-homocitrullyl, beta-Ala, etc; H = L-Leu, N(R12)-L-Leu, Gly, sarcosyl, Pro, L-Val, L-cyclohexylalanyl, or N-alpha-(R12)-L-cyclohexylalanyl; R12 = H or 1-6C alkyl; I = L-citrullyl, L-homocitrullyl, L-His, L-(N-epsilon-isopropyl)lysyl, L-Arg, N-alpha-(R12)-L-Arg, L-homoarginyl, L-2-amino-6-Ng-ethylguanidinohexanoyl or L-2-amino-6-Ng, Ng-diethylguanidinohexanoyl; J = L-Pro, 4-hydroxy-L-prolyl, L-pipecolyl, L-azetidinyl, L-2,8-tetrahydroisoquinoline-2-carbonyl, N(R12)-L-Leu, sarcosyl, Gly, or N(R12)-L-Ala; K = NHEt, D-alanylamide, D-alanyl (OH), D- or L-glutamyl (OH), N(R12)-L- or D-alanylamide, sarcosamide, D-serylamide, azaglycylamide or glycylamide; provided that when K is NHEt then J is L-Pro.
USE - (I) are **LHRH antagonists** and are useful for suppressing levels of **gonadotropins** and

androgens in mammals. They may be used e.g. in treatment of benign prostatic hyperplasia, breast, prostate or **ovary** tumours, cryptorchidism, hirsutism, gastric motility disorders, dysmenorrhoea or endometriosis, to delay puberty, or in contraception. **Admin**. is, e.g. oral, parenteral, vaginal, rectal, transdermal or intranasal.
Dwg.0/0

ABEQ US 5413990 A UPAB: 950626
Nine cpds. or their salts are claimed e.g. N-glycosyl-D2-Nal-D4ClPhe-D3Pal -Ser-NMeTyr-D-Cit-Leu-Arg-Pro- DAlaNH2 and N-formyl-D2Nal-D4ClPhe-D3Pal -Ser-NMeTyr-DGt-Leu-Arg- Pro-DAlaNH2.
USE - As potent LHRH antagonists for suppressing the levels of sex hormones, e.g. gonadotropins and androgens. Admin. is 0.01-10 mg/kg/day, pref. 0.1-5.0 mg/kg/day. Administration may be parenteral (e.g. subcutaneous, intramuscular or intravenous), vaginal, rectal, oral, buccal or intranasal.
Dwg.0/0

ABEQ US 5502035 A UPAB: 960503
A peptide having structure I or pharmaceutically acceptable salt thereof. X = dihydro-shikimyl, 2-furoyl, 3-furoyl, tetrahydro-furo-2-yl, tetrahydro- furo-3-yl, (thien-2-yl) carbonyl, (thien-3-yl) carbonyl, (tetrahydrothien-2-yl) carbonyl, (tetrahydrothien-3-yl) carbonyl, pyrrol-2-yl) carbonyl, (pyrrol-3-yl) carbonyl, prolyl, N-acetyl-prolyl, 3-(indolin-3-yl) propionyl, (indolin-3-yl) acetyl, (indolin-2-yl) carbonyl, (indolin-3-yl) carbonyl, benzo[b]fur-2-yl) carbonyl, (dihydrobenzo [b] fur-2-yl) carbonyl, (tetrahydropyran-2-yl) carbonyl, (tetrahydropyran-3-yl) carbonyl, (piperidin- 3-yl) carbonyl, (N-acetyl piperidin-3-yl) carbonyl, nicotinyl opt. substd with 1-6C alkyl, 1-6C alkoxy, halo, or OH, isonicotinyl opt. substd with 1-6C alkyl, 1-6C alkoxy, halo, or OH, picolinoyl, 2-, 3- or 4-quinolinecarbonyl opt. substd with 1-6C alkyl, 1-6C alkoxy, halo, or OH; salicyl, shikimyl, or p-toluenesulphonyl; A is absent or is D-alanyl, 3-aminopropionyl, 4-aminobutyryl, 5-aminovaleryl, 6-amino-hexanoyl, 7-amino- heptanoyl, 8-aminooctanoyl, 11-aminoundecanoyl, azaglycyl,
glycyl, sarcosyl, or D-seryl; B = D-phenylalanyl, D-3-(4-chlorophenyl) alanyl, D-3-(4-fluoro- phenyl) alanyl, D-3-(quinolin-3-yl) alanyl, sarcosyl, glycyl, azaglycyl, D-3,3-diphenyl- alanyl, Nalpha-methyl- D-3-(naphth-2-yl) alanyl, or D-3-(naphth-2-yl) alanyl; C = D-3-(4-chlorophenyl) alanyl, D-3,3-diphenylalanyl, D-3-(4-fluorophenyl) alanyl, D-3-(naphth-2-yl) alanyl, D-phenyl- alanyl, or D-3-(quinolin-3-yl) alanyl; D = D-alanyl, D-3-(benzo [b] thien-2-yl) alanyl, glycyl, D-3-(naphth-1-yl)alanyl, D-3-(pyrid-3-yl)alanyl, D-3-(quinolin-3-yl) alanyl, or D-3-(thiazol-2-yl) alanyl; E = glycyl, L-seryl, L-homoseryl, L-seryl(O-benzyl), or Nalpha(R)-L seryl where R is 1-4C alkyl; F = Nalpha(R1)-alanyl, Nalpha(R1)- (3-(4-(3-amino-1,2,4-triazol-5-yl) amino) phenyl) alanyl, Nalpha(R1)-(3-(4-((3-amino-1,2,4-triazol- 5-amino) methyl) phenyl) alanyl, Nalpha(R1)-(3-(4-(3-amino- 1,2,4-triazol-5-yl) amino) cyclohexyl) alanyl, Nalpha(R1)-(3-(4-(nicotinyl) amino) cyclohexyl) alanyl, Nalpha(R1)-(N-e-nicotinyl) lysyl, Nalpha(R1)-(N-e-(3-amino-1,2,4-triazol-5-yl) lysyl, Nalpha(R1)-3- (4-nitrophenyl) alanyl, Nalpha(R1)-3-(4-aminophenyl) alanyl, Nalpha(R1)-3-(4-aminocyclohexyl) alanyl, Nalpha(R1)-tyrosyl, Nalpha(R1)-tyrosyl (O-methyl), Nalpha(R1)- phenylalanyl, Nalpha(R1)-cyclohexyl- alanyl, Nalpha(R1)-glycyl, Nalpha(R1)-arginyl, Nalpha(R1)-histidyl, or Nalpha(R1)-homoarginyl; R1 = H or 1-4C alkyl; G = glycyl, D-citrullyl, D-homocitrullyl, beta-alanyl, D-lysyl (N-epsilon glycyl

nicotinyl), D-lysyl (N-epsilon azaglycyl nicotinyl), D-lysyl (N-epsilon shikimyl), D-lysyl (N-epsilon glycyl shikimyl), D-lysyl (N-epsilon azaglycyl shikimyl), D-lysyl (N-epsilon dihydroshikimyl), D-lysyl (N-epsilon glycyl dihydro- shikimyl), D-lysyl (N-epsilon azaglycyl dihydro- shikimyl), D-lysyl (N-epsilon fur-2-oyl), D-lysyl (N-epsilon glycyl fur-2-oyl), D-lysyl (N-epsilon azaglycyl fur-2-oyl), D-lysyl (N-epsilon tetrahydrofur-2-oyl), D-lysyl (N-epsilon glycyl tetrahydrofur-2-oyl), D-lysyl (N-epsilon azaglycyl tetrahydro- fur-2-oyl), D-lysyl (N-epsilon- (3-amino-1,2,4-triazol-5-yl) amino), or D-3-(4-(3-amino- 1,2,4- triazol-5-yl) amino) phenyl-alanyl; H = L-leucyl; Nalpha(R2)- L-leucyl; glycyl; sarcosyl; prolyl; L-valyl; L-cyclohexylalanyl; or Nalpha(R2)-L-cyclohexyl-alanyl; R2 = H or 1-6C alkyl; I = L-citrullyl; L-homocitrullyl; L-histidyl; L-(N-epsilon- isopropyl) lysyl; L-arginyl; Nalpha(R3)-L-arginyl; L-homoarginyl; L-2-amino- 6-Ng-ethyl-guanidinohexanoyl; or L-2-amino-6-Ng,Ng- diethyl- guanidinohexanoyl; J = L-prolyl; 4-hydroxy-L-prolyl; L-pipecolyl; L-azetidinyl; L-2,8-tetrahydro- isoquinoline-2-carbonyl, Nalpha(R3)- L-leucyl; sarcosyl; glycyl; or N(R1)-L-alanyl; R3 = H or 1-6C alkyl; and K = -NH(CH2CH3) or D-alanylamide, D-alanyl- (OH), D-glutamyl(OH), L-glutamyl(OH), Nalpha(R3)-L- alanylamide, Nalpha(R3))-D-alanylamide, sarcosamide, D-serylamide, azaglycylamide, or glycylamide, with the proviso that when K = -NH(CH2CH3) then J = L-prolyl.
Dwg.0/0

L131 ANSWER 4 OF 47 TOXLIT
AN 95:105812 TOXLIT
DN CA-123-189355S
TI Ovulation control by regulating nitric oxide levels.
AU Garfield RE; Yallampalli C
SO (1995). PCT Int. Appl. PATENT NO. 95 15753 06/15/95 (Board of Regents, University of Texas System).
CY United States
DT Patent
FS CA
LA English
OS CA 123:189355
EM 9511
AB Inhibition of **ovulation** in a female may be achieved by **administering** a nitric oxide synthase inhibitor, alone or in combination with one or more of a progestin, an estrogen, and an **LH-RH antagonist**, thereby preventing conception. The stimulation of **ovulation** in a female may be achieved by **administering** a nitric oxide source, optionally in further combination with one or more of clomiphene, a **gonadotropin**, and an LH-RH agonist. Thus, 27 days old immature rats were injected with 4 IU of pregnant mare's serum **gonadotropin** on day on. Two days later rats were injected with 40 mg of NG-nitro-L-arginine Me ester at 12 AM and 3 PM and animals were sacrificed one day later and examd. for the **ovulatory** response by counting the no. of Graafian follicles 3 and corpora lutea 5 in the **ovaries**. The no. of Graffian follicles and corpora lutea was 9.7 and 0.7 resp. as compared to 1.0 and 10.0 for the controls.

L131 ANSWER 5 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 3
AN 95:536681 BIOSIS
DN 98550981
TI Active immunization against LHRH alone or combined with LHRH-analogue

treatment impedes growth of androgen-dependent prostatic carcinoma.
AU Ladd A; Walfield A; Tsong Y-Y; Thau R
CS Vaccine Res. Inc., 148 Neptune Ave., Brooklyn, NY 11235, USA
SO American Journal of Reproductive Immunology 34 (3). 1995. 200-206.
ISSN: 1046-7408
LA English
AB Problem: To determine whether active immunization against LHRH can serve as treatment for androgen-dependent prostatic carcinoma. Method: Male rats of Copenhagen times Fisher strain, implanted with Dunning R-3327 prostatic carcinoma cells were either immunized against **LHRH**, treated with **LHRH-antagonist**, or received a combined treatment of active immunization against **LHRH** and **LHRH-antagonist**. Results: Testicular histology was consistent with **infertility** in all treatment groups. The rate of tumor growth was inhibited by all three treatment regimens. Tumor size increased by 3.8 +- 1.4 cm-2 in the **LHRH-antagonist** group, 3.2 +- 1.1 cm-2 in the immunized group, and 1.0 +- 0.4 cm-2 in the combined treatment group, as compared to 8.2 +- 2.6 cm-2 in non-treated control group. Conclusion: **LHRH-antagonist administration** combined with immunization against LHRH appeared to exert a synergistic effect. This may be due to the blockade of prostatic LHRH-like receptors by the antagonist, while androgen depletion was rapidly achieved by **LHRH-antagonist**, and maintained by continued **gonadotropin** suppression caused by active immunization against **LHRH** once **antagonist** treatment had been discontinued.

L131 ANSWER 6 OF 47 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.DUPLICATE 4
AN 95201656 EMBASE
TI [Effect of different treatments on hormone secretion and cystic ovarian morphology in the rat treated with RU486].
EFECTO DE DIFERENTES TRATAMIENTOS SOBRE LA SECRECION HORMONAL Y LA MORFOLOGIA OVARICA QUISTICA DE LA RATA TRATADA CON RU486.
AU Ruiz A.; Aguilar R.; Tebar M.; Gaytan F.; Sanchez-Criado J.E.
CS Departamento de Fisiologia, Facultad de Medicina, Universidad de Corboda, Avda. Menendez Pidal, s/n, 14004 Cordoba, Spain
SO Endocrinologia, (1995) 42/5 (150-155).
ISSN: 0211-2299 CODEN: ENDCDP
CY Spain
DT Journal
FS 003 Endocrinology
037 Drug Literature Index
LA Spanish
SL Spanish; English
AB Rats treated with the antiprogestagen RU486 (RU) present a cystic **ovarian** picture compatible endocrinologically and morphologically with the human polycystic **ovarian** syndrome (PCOS). The **administration** of an **antagonist** of **LHRH** to rats deprived of the actions of progesterone by the antiprogestagen, reduced the high serum levels of LH, testosterone (T) and estradiol (E2), as well as the quotients LH/FSH and T/E2; the **ovary** decreased in size and presented a lower number of cysts, a lesser degree of atresia and a reactivation of follicular growth. A similar effect was observed in the rats treated with the antiestrogen tamoxifen. The **administration** of the antiandrogen flutamide increased the endocrinological changes, whereas it decreased, in part, the morphological ones. The reduction in the serum levels of prolactin by the dopaminergic agonist

bromocriptine failed to normalize the secretion of **gonadotropins** and the production of **ovarian** steroids, although the **ovary** showed a decrease in the number of cysts and the degree of atresia, as well as an increase in follicular growth. Finally, the **administration** of human FSH (hFSH) to rats treated with RU increased the peripheral levels of E2 without altering the remaining endocrine parameters. However, hFSH originated an important decrease in the degree of atresia and an intense reactivation in follicular growth in the **ovary**. Similar therapeutic measures used in patients with polycystic **ovarian** syndrome (PCOS) produce endocrinological and morphological changes very like those described above in the rats treated with RU. This, together with the existing similarities between the anovulatory cystic picture in the animal model and the patients with PCOS, confirms the value of rats treated with the antiprogestagen RU486 as a model for studying this disease, as well as the importance of progesterone in developing and maintaining the condition of **ovarian** cysts.

L131 ANSWER 7 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 5
AN 95:251399 BIOSIS
DN 98265699
TI Evidence of a permissive effect of extra-ovarian steroids on the release of FSH at early estrus in rats lacking inhibin secretion or action.
AU Tebar M; Bellido C; Sanchez-Criado J E
CS Dep. Physiol., Fac. Med., Avda. Menendez Pidal s/n, Univ. Cordoba, 14004 Cordoba, Spain
SO Neuroendocrinology Letters 17 (1). 1995. 21-27. ISSN: 0172-780X
LA English
AB The **administration** (sc) of 1 mg of a **LHRH** **antagonist** (LHRHa) (Organon, Oss, The Netherlands) to 4-day cyclic rats at 0900 h in proestrus blocked the preovulatory (proestrous 1830 h) release of **gonadotropins** (LH and FSH) and abolished the secondary (estrous 0200 h) release of FSH. The **administration** (sc) of 4 mg of either antiprogestagen RU486 (Roussel-Uclaf, Romainville, France) or antiprogestagen ZK299 (Schering, Berlin, Germany) at 0900 h in proestrus blunted the preovulatory release of **gonadotropins** and abolished the secondary release of FSH. The effect of the LHRHa on the secondary surge of FSH in cyclic rats was totally reversed by an **ovulatory** (sc) injection (10 IU) of hCG at 1700 h in proestrus. Injections of 3, 5 or 10 mg (sc) of progesterone at 1500 h in proestrus or of 0.5 ml (iv) of an anti-inhibin serum at 1900 h in proestrus alone reversed, although only in part, the effect of LHRHa on the serum concentration of FSH at 0200 h in estrus. The combination of progesterone and anti-inhibin serum injections to LHRHa-treated rats completely restored the secretion of FSH at early estrus. The removal of **ovarian** progesterone and inhibin by **ovariectomy** (OVX) at 1500 h on proestrus did not affect the serum concentration of FSH at 0200 h on estrus either in oil- or RU486-treated rats. The injection of progesterone to OVX-rats did not affect the serum concentrations of FSH or LH at 0200 h in estrus. These combined observations suggest that, in the rat, the preovulatory LH-dependent drop in **ovarian** inhibin secretion, together with the actions of steroids, which can be blocked by the **administration** of either RU486 or ZK299, during proestrous afternoon and evening allow the secondary release of FSH during early estrus. These steroids (progesterone and/or glucocorticoids) come from extraovarian tissues (most probably the

adrenal glands).

L131 ANSWER 8 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 6
AN 94:59630 BIOSIS
DN 97072630
TI The chronic intracerebroventricular infusion of interleukin-1-beta alters the activity of the hypothalamic-pituitary-gonadal axis of cycling rats: II. Induction of pseudopregnant-like corpora lutea.
AU Rivier C; Erickson G
CS The Clayton Found. Lab. Peptide Biol., The Salk Inst., 10010 North Torrey Pines Road, La Jolla, CA 92037, USA
SO Endocrinology 133 (6). 1993. 2431-2436. ISSN: 0013-7227
LA English
AB The acute **administration** of interleukin-1-beta (IL-1-beta) into the brain ventricles of rats has been shown to cause a significant decrease in plasma LH levels, a phenomenon primarily mediated through inhibition of LHRH release. However, there are no studies of the long-term consequences of IL-1-beta injected intracerebroventricularly on the hypothalamic-pituitary-gonadal axis. In particular, we became interested in determining whether IL-1-beta exerts deleterious effects on **reproductive** parameters, and to what extent they might be caused by a lowering of circulating **gonadotropins**. In the present experiments, we therefore investigated the effects of the infusion of IL-1-beta to intact cycling female rats and compared them to those observed in rats injected with a potent **LHRH antagonist**. Although blockade of **LHRH** receptors caused a modest and delayed inhibition of progesterone secretion, infusion of IL-1-beta (4 ng/h for 4-6 days) was accompanied by persistent and significant increases in plasma P4 levels. In these rats, the pattern of PRL release was erratic, with low values during the morning and generally extremely elevated values during the night. The volume of the corpora lutea-I (CL-I) of rats exposed to IL-1-beta, but not to the vehicle or the **LHRH antagonist**, was significantly increased, and the lutein cells showed extensive hypertrophy. These results indicate that prolonged infusion of IL-1-beta into the brain of cycling rats blocks luteolysis in newly formed CL. These changer, were not present in rats injected with the **LHRH antagonist**, suggesting that they were not primarily related to decreases in **gonadotropin** secretion. We propose that the high plasma PRL levels may play a role in the changes in **ovarian** activity which we observed, through other mechanisms, such as sustained increases in adrenal epinephrine and/or glucocorticoids, may also be involved. These findings indicate a novel role for central IL-1-beta in the prevention of luteolysis and the transformation of the CL of the cycle into a CL of pseudopregnancy.

L131 ANSWER 9 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 7
AN 93:325953 BIOSIS
DN BA96:34303
TI DIFFERENTIAL GONADOTROPHIN RESPONSES TO N METHYL-D L-ASPARTATE IN METESTROUS PROESTROUS AND OVARIECTOMIZED RATS.
AU LUDERER U; STROBL F J; LEVINE J E; SCHWARTZ N B
CS DEP. NEUROBIOL. PHYSIOL., 2153 SHERIDAN RD., NORTHWEST. UNIV., EVANSTON, IL 60208, USA.
SO BIOL REPROD 48 (4). 1993. 857-866. CODEN: BIREBV ISSN: 0006-3363
LA English
AB Peripheral **administration** of N-methyl-D,L-aspartate (NMA), an analogue of the excitatory amino acid aspartate, elicits LH and prolactin (PRL) release in rats, most likely by increasing endogenous

releasing-hormone secretion. These experiments were carried out to assess the degree to which NMA stimulates FSH and to analyze the relationship between endocrine status and responsiveness to NMA in female rats, in contrast to male rats, as described in the companion paper [Biol **Reprod** 48:000-000]. In experiment 1, estrous rats (n = 10) and diestrous rats (n = 10) and in experiment 2, estrous rats (n = 11) and rats **ovariectomized** (OVX) 8 days previously (n = 10) were fitted with atrial catheters and injected s.c. with 100 .mu.g of an **LHRH antagonist** or vehicle at 2100 h. Starting at 0900 h the next day (metestrus, proestrus, or Day 9 post-OVX), blood was withdrawn every 10 min for 3 h. Each animal received i.v. 5 mg NMA after the first hour and i.v. 500 ng LHRH after the second hour. NMA significantly increased LH in metestrous and proestrous females, and **LHRH antagonist** blunted the increases. In OVX females, LH decreased after NMA. FSH was not affected by NMA in any group. PRL increased after NMA in proestrous and metestrous animals. LHRH caused surge-like LH and small FSH increases in vehicle groups; these increases did not differ in amplitude between intact and OVX animals and were blunted by pretreatment with **LHRH antagonist**. In experiment 3, 10 diestrous rats were fitted with atrial catheters and were serially bled at 2-h intervals from 1200 h on the following day (proestrus) until 0600 h on estrus morning. After the first sample the animals were injected s.c. with 0.2 mg/kg MK801, a noncompetitive NMA receptor antagonist, or with saline. Four of the 5 saline-treated animals exhibited surges of LH and FSH as well as elevated progesterone levels, with LH and progesterone peaking at 2000 h. Five of 5 MK801-treated animals failed to have elevated LH, FSH, or progesterone levels at any time point. These data demonstrate that LHRH mediates the LH response to NMA in rats and that endogenous NMA receptor binding may be necessary for the preovulatory **gonadotropin** surges. The lack of FSH responses to NMA during periods of low level **gonadotropin** secretion suggests that physiological increments in endogenous LHRH secretion sufficient to induce a pulse of LH are insufficient to stimulate pulse-like FSH release. Comparison of metestrous and proestrous NMA responses suggests that elevated proestrous estradiol levels do not enhance the releasability of LHRH by NMA, while the suppression of LH levels following NMA in OVX rats suggests that in the absence of **ovarian** feedback the inhibitory effects of NMA on LHRH release predominate over its stimulatory effects.

L131 ANSWER 10 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 8
AN 94:21821 BIOSIS
DN 97034821
TI Inhibitory effect of a highly potent antagonist of LH releasing hormone (SB-75) on the pituitary gonadal axis in the intact and castrated rat.
AU Ayalon D; Farhi Y; Comaru-Schally A M; Schally A V; Eckstein N; Vagman I; Limor R
CS Timsit Inst. Reproductive Endocrinology, Ichilov Hosp., 6 Weizmann Street, Tel Aviv 64239, ISR
SO Neuroendocrinology 58 (2). 1993. 153-159. ISSN: 0028-3835
LA English
AB The biological potency of the new, highly potent antagonist (AC-D-Nal (2)-1, D-Phe(4Cl)-2, D-Pal(3)-3, D-Cit-6, D-Ala-10) LH-RH (SB-75) on the pituitary-gonadal system of female castrated and intact **ovulating** rats was tested. **Administration** of a single dose (50-100 mu-g/kg BW) of the antagonist SB-75 inhibited effectively the elevated **gonadotrophin** levels for 48 h.

Pituitary LH and FSH content was not affected by SB-75 treatment. When **administered** in the early afternoon of the proestrus to intact cycling rats, SB-75 blocked the preovulatory LH surge as well as the primary and secondary FSH surges. However, the secondary FSH surge was not affected by SB-75 treatment when **administered** on the evening of proestrus suggesting its independence from the LH-RH mechanism. A group of **ovariectomized** rats was chronically treated with D-Trp-6-LH-RH after having been pretreated by **administration** of a single dose of the antagonist. The initial stimulatory release of LH and FSH initiated by injection of the LH-RH agonist was significantly reduced by pretreatment with the **LH-RH antagonist**. We conclude that the **LH-RH antagonist** SB-75 may be used effectively in the field of **reproductive** dysfunction and endocrinological oncology and may become an invaluable physiological probe in studying the hormonal dynamics of the **reproductive** endocrine axis.

L131 ANSWER 11 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 9
AN 93:185155 BIOSIS
DN BA95:95605
TI CHANGES IN PITUITARY SECRETION DURING THE EARLY POSTNATAL PERIOD AND ANOVULATORY SYNDROME INDUCED BY NEONATAL OESTROGEN OR ANDROGEN IN RATS.
AU PINILLA L; TRIMINO E; GARNELO P; BELLIDO C; AGUILAR R; GAYTAN F; AGUILAR E
CS DEP. PHYSIOL., BIOL. SECT., SCH. MED., UNIV. CORDOBA, CORDOBA, SPAIN.
SO J REPROD FERTIL 97 (1). 1993. 13-20. CODEN: JRPFA4 ISSN: 0022-4251
LA English
AB The following experiments were performed: (i) concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin in plasma were measured at 2, 5, 8, 10 and 15 days in female Wistar rats treated on the first day of life with 100 .mu.g oestradiol benzoate or vehicle; (ii) females injected on day 1 with 100 .mu.g of oestradiol benzoate or 1 mg of testosterone propionate and from day 1 to day 10 or 15 with FSH and LH were killed on day 90; (iii) females injected from day 1 to day 10 15 with prolactin or vehicle were killed on day 90; (iv) females injected on day 1 with oestradiol benzoate and from day 1 to day 15 with a luteinizing-hormone-releasing hormone (LHRH) agonist were killed on day 90; (v) groups of females injected on day 1, 4, 7, 10, 13 and 16 with an **LHRH antagonist** were killed on day 90.
Onset of puberty, vaginal cycles, organ weights and hormonal plasma concentrations were measured. Females treated on the first day of life with 100 .mu.g oestradiol showed inhibition of **gonadotrophin** secretion and stimulation of prolactin secretion during the neonatal period. Females injected on the first day of life with oestradiol benzoate or testosterone propionate showed, in adulthood, anovulation, **ovarian** atrophy, reduced FSH plasma concentrations, increased prolactin plasma concentrations and reduced pituitary prolactin content. These alterations were due neither to blocked **gonadotrophin** secretion nor to stimulated prolactin secretion observed immediately after steroid injection, since: (i) development of the anovulatory syndrome was not blocked by the **administration** of exogenous **gonadotrophins** or LHRH-agonist; and (ii) blockade of **gonadotrophin** secretion immediately after birth with an **LHRH antagonist** or neonatal injection of prolactin did not induce the anovulatory syndrome. It is concuded that anovulation induced by **administration** of neonatal steroid

was mediated neither by the early inhibition of **gonadotrophin** secretion nor by the stimulation of prolactin secretion.

L131 ANSWER 12 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 10
AN 92:481130 BIOSIS
DN BA94:112505
TI PROPERTIES OF A POTENT LHRH ANTAGONIST ORG 30850 IN FEMALE AND MALE RATS.
AU DECKERS G H J; DE GRAAF J H; KLOOSTERBOER H J; LOOZEN H J J
CS ORGANON SCIENTIFIC DEVELOPMENT GROUP, P.O. BOX 20, 5340 BH OSS, NETHERLANDS.
SO J STEROID BIOCHEM MOL BIOL 42 (7). 1992. 705-712. CODEN: JSBBEZ ISSN: 0960-0760
LA English
AB Org 30850 (Ac-DpClPhe1,2D-Bal3,D-Lys6,D-Ala10-LHRH) is a novel **LHRH antagonist**, which is being developed for the treatment of hormone-dependent disorders. The activities of this compound with respect to its endocrinological properties and side-effects were tested in rats and the results were compared with one of the first **LHRH antagonists**: Ac-D-pClPhe1,2,D-Trp3,D-Arg6,D-Ala10-LHRH (Org 30276). A single subcutaneous (s.c.) dose of 0.3 .mu.g/kg Org 30850 **administered** to rats in pro-estrus gave inhibition of **ovulation** in approx. 50% of the rats, whereas Org 30276 was approx. 4 times less potent. The effect of a single s.c. injection of Org 30850 on testosterone levels in young adult male rats was also studied. The **administration** of 250 .mu.g/kg or higher of Org 30850 induced a significant decrease in testerone levels after 3 h, their effect last for at least 48 h. Treatment of female rats for 14 days with a daily dose of 12 .mu.g/kg Org 30850 decreased statistically significantly uterine and **ovarian** weights. At a daily dose of 50 .mu.g/kg Org 30850 completely suppressed estrous cycles and significantly decreased estradiol and FSH serum levels. The LH levels were below the detection level in both control and treated animals on the (expected) second day of di-estrus. Treatment of male rats for 14 days (25-200 .mu.g/kg) resulted in a dose-dependent reduction of the gonads, accessory sex organs, testosterone levels and **gonadotrophins**. The decrease in gonadal function in both sexes was reversible since the females proved to be as **fertile** as the controls 6 weeks after the last rreatment and an almost complete recovery of the weight of testes, seminal vesicles and ventral prostate was observed in the males 4 weeks after cessation of treamtent. In contrast to Org 30276, Org 30850 exerted very slight irritation at the site of injection and no edematous reactions in the extremities at a daily dose of up to 8 mg/kg in male rats. It is concluded that Org 30850 is a very potent **LHRH antagonist** without edematous reactions and with a more favourable therapeutic index than Org 30276.

L131 ANSWER 13 OF 47 TOXLIT
AN 91:40495 TOXLIT
DN CA-114-178505D
TI Antide-induced suppression of pituitary gonadotropin and ovarian steroid secretion in cynomolgus monkeys: premature luteolysis and prolonged inhibition of folliculogenesis following single treatment.
AU Gordon K; Williams RF; Danforth DR; Hodgen GD
CS Jones Inst. Reprod. Med., East. Virginia Med. Sch., Norfolk
SO Biol. Reprod, (1991). Vol. 44, No. 4, pp. 701-6.
CODEN: BIREBV. ISSN. 0006-3363.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 114:178505
EM 9106
AB **Administration** of high-doses of the **LH-RH antagonist** Antide to **ovariectomized** monkeys results in rapid, prolonged, and reversible inhibition of **gonadotropin** secretion. It was examd. whether similar long-term control would be manifested in the menstrual cycle of intact primates. Antide **administration** at a dose of either 3.0 or 18.0 mg/kg induced rapid suppression of bioassayable LH concns., pptg. a concurrent fall in serum progesterone concns. from .apprx.7 ng/mL on the day of injection to .apprx.0.5 ng/mL by 2 days post-treatment, resp. This Antide-induced luteolysis was accompanied by the premature onset of menses within 3 days. The next menses following Antide **administration** was delayed. Ultimately, folliculogenesis culminating in normal follicular-phase estradiol prodn., **ovulation**, and subsequent normal luteal-phase progesterone prodn. did occur in all treated monkeys. Menses resumed 54 and 75 days after treatment with 3.0 and 18.0 mg/kg Antide, resp. No allergic cutaneous or peripheral reactions were seen, even at the highest dose of Antide. Thus, the long duration of action of high-dose Antide reported earlier in **ovariectomized** monkeys is also demonstrated in intact primates. These findings, along with the apparent absence of histamine-release effects even at high doses, suggest that Antide is a GnRH antagonist deserving clin. evaluation for management of gonadal steroid-dependent endocrinopathies and for potential contraceptive applications.

L131 ANSWER 14 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 11
AN 91:202922 BIOSIS
DN BA91:106147
TI INCREASED CONCENTRATIONS OF IMMUNOREACTIVE INHIBIN DURING CONCEPTION CYCLES IN THE MARMOSET MONKEY SUPPRESSION WITH AN LHRH ANTAGONIST AND CLOPROSTENOL.
AU WEBLEY G E; KNIGHT P G; GIVEN A; HODGES J K
CS MRC/AFRC COMPARATIVE PHYSIOL. GROUP, INST. ZOOL., REGENT'S PARK, LONDON NW1 4RY.
SO J ENDOCRINOL 128 (3). 1991. 465-474. CODEN: JOENAK ISSN: 0022-0795
LA English
AB Peripheral concentrations of immunoreactive (ir) inhibin have been measured during the **ovarian** cycle and early pregnancy in the marmoset monkey. Blood samples were taken (three per week) during conception (n = 6) and non-conception (n = 5) cycles. Ir-inhibin was measured by radioimmunoassy using an antiserum raised against a synthetic peptide fragment of the .alpha. subunit of human inhibin. Monomeric bovine .alpha. subunit and 32 kDa bovine inhibin were used as tracer and standard respectively. In all animals low concentrations of ir-inhibin were recorded during the follicular phase (40-60 .mu.g/l) of the cycle. After **ovulation**, ir-inhibin concentrations increased but the peak concentrations attained differed between conception and non-conception cycles. In non-pregnant animals ir-inhibin concentrations reached a maximum of 242 .+-. 16 .mu.g/l on days 12/13 after **ovulation**. In pregnant animals ir-inhibin concentrations were significantly ($P < 0.05$) higher (1.8-fold) than in non-pregnant animals on days 8/9 after **ovulation**, and reached a maximum value of 636 .+-. 141 .mu.g/l on days 20/21 after **ovulation**.

Administration of an **LHRH antagonist** during the luteal phase on days 6-8 after **ovulation** resulted in a significant ($P < 0.05$) decrease in progesterone and ir-inhibin concentrations within 4 and 8 h respectively. This was prevented by co-**administration** with human chorionic **gonadotrophin**. **Administration** of cloprostenol to pregnant animals between days 17 and 20 after **ovulation** halved the initial concentrations of both inhibin and progesterone within 1.5 h. The increase in plasma ir-inhibin concentrations in the luteal phase and the apparent similarity in control of ir-inhibin and progesterone supports a luteal source of ir-inhibin in both conception and non-conception cycles. The higher levels of ir-inhibin from days 8/9 after **ovulation** in conception cycles were not related to any detectable increase in peripheral concentrations of chorionic **gonadotrophin** and occurred at least 4 days before the expected time of implantation. This suggests a role for the conceptus in inhibin secretion which may involve the release of an embryo message before implantation.

L131 ANSWER 15 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 12
AN 91:157906 BIOSIS
DN BA91:83706
TI COMPARISON OF THE LUTEOLYTIC ACTION OF GONADOTROPIN-RELEASING HORMONE ANTAGONIST AND CLOPROSTENOL AND THE ABILITY OF HUMAN CHORIONIC GONADOTROPIN AND MELATONIN TO OVERRIDE THEIR LUTEOLYTIC EFFECTS IN THE MARMOSET MONKEY.
AU WEBLEY G E; HODGES J K; GIVEN A; HEARN J P
CS MRC/AFRC COMPARATIVE PHYSIOL. GROUP, INST. ZOOL., REGENT'S PARK, LONDON NW1 4RY.
SO J ENDOCRINOL 128 (1). 1991. 121-130. CODEN: JOENAK ISSN: 0022-0795
LA English
AB The effects of the luteolytic and luteotrophic agents cloprostenol, human chorionic **gonadotrophin** (hCG) and melatonin on the corpus luteum have been investigated in marmoset monkeys treated with an **LHRH antagonist** to reduce endogenous LH secretion. This has allowed the effects of these agents to be investigated in the absence of the principal endogenous luteotrophin. **Administration** of the **LHRH antagonist** ([N-acetyl-D.beta.Nal1-D-pCl-Phe2-D-Phe3-D-Arg6-Phe7-Arg8-D-Ala10]NH2-LHRH) or cloprostenol between days 7 and 11 after **ovulation** (preimplantation) resulted in luteolysis. A significant ($P < 0.05$) decrease in progesterone concentrations had occurred by 4 h after **administration** of the **LHRH antagonist** and was indeed preceded by a fall in LH concentrations. Co-**administration** of hCG with the **LHRH antagonist** prevented the fall in progesterone. In contrast, **administration** of cloprostenol resulted in an immediate fall in progesterone concentrations, to less than half the initial level within 1 h, and co-**administration** with hCG did not prevent the fall. **Administration** of hCG stimulated progesterone production when given 8 h after the **LHRH antagonist** but not after 24 h. Cloprostenol prevented the stimulation by hCG. Co-**administration** of melatonin with the **LHRH antagonist** did not prevent the decrease in progesterone concentrations. Melatonin was also not effective in preventing the fall in progesterone induced by cloprostenol. However, co-**administration** of melatonin and cloprostenol between days 17 and 21 after **ovulation** (postimplantation) significantly ($P < 0.05$) delayed the fall in progesterone seen with cloprostenol alone. These results suggest that while the **LHRH**

antagonist and cloprostenol have different sites of action their effect is similar at the corpus luteum, that is in depriving the corpus luteum of luteotrophic support. The results also suggest that melatonin may be able to influence the luteolytic action of cloprostenol but that its effect varies with the stage of the cycle. The physiological role for such an action, if any, remains unknown.

L131 ANSWER 16 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 13
AN 90:267257 BIOSIS
DN BA90:9343
TI TESTICULAR WEIGHT TUBULAR DIAMETER AND NUMBER OF SERTOLI CELLS IN RATS ARE DECREASED AFTER EARLY PREPUBERTAL ADMINISTRATION OF AN LHRH-ANTAGONIST THE QUALITY OF SPERMATOZOA IS NOT IMPAIRED.
AU VAN DEN DUNGEN H M; VAN DIETEN J A M J; VAN REES G P; SCHOEMAKER J
CS DEP. OBSTETRICS AND GYNAECOL., VRIJE UNIV., AMSTERDAM, NETHERLANDS.
SO LIFE SCI 46 (15). 1990. 1081-1090. CODEN: LIFSAK ISSN: 0024-3205
LA English
AB To suppress **gonadotropin** secretion during the sensitive period in development of the testes, immature male rats were treated with an antagonist of luteinizing hormone-releasing hormone (LHRH; ORG.30276) from postnatal days 6-15. Previously, it has been demonstrated that this treatment results in delayed pubertal development, decreased testicular weight, impaired **fertility** and adult sexual behavior. In the present experiments it was investigated whether the decreased testicular weight was correlated with morphological changes in the testis. Also, by using an artificial insemination technique, the biological activity of spermatozoa of adult male rats, treated during early prepuberty with the **LHRH antagonist** (**LHRH**-A), was tested. The present results demonstrated a decrease in the diameter of the testicular tubuli of LHRH-A-treated rats. The number of Sertoli cells per tubular cross-section was also smaller. But qualitatively no differences could be observed in the testis. All stages of maturation of the seminiferous epithelium were equally frequently represented in LHRH-A-treated males compared with controls. Artificial insemination using spermatozoa obtained from the epididymis of LHRH-A-treated rats, resulted in a pregnancy rate of 100%, similar to the control rate. From the present data, we conclude that the **infertility** in adult male rats, treated with an **antagonist** to **LHRH** during prepurbertal life, does not result from malfunction in the maturational processes in the germinal cells and the testes as a whole, despite the observation of changes in the testicular morphology. The **infertility** of LHRH-A-treated male rats can be explained by the observed impairment of sexual behavior. We suggest, that a central action of the **antagonist** of **LHRH** when **administered** to immature male rats may lead to permanent changes in the development of sexual behavior.

L131 ANSWER 17 OF 47 TOXLIT
AN 90:60104 TOXLIT
DN CA-113-017979A
TI A 90-day subcutaneous toxicity and fertility study of a LHRH antagonist in rats.
AU Sundaram K; Didolkar AK; Keizer-Zucker A; DeJesus W; Rivier J; Vale W; Bardin CW
CS Cent. Biomed. Res., Population Counc., New York
SO Fundam. Appl. Toxicol, (1990). Vol. 14, No. 4, pp. 734-44. CODEN: FAATDF. ISSN. 0272-0590.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 113:17979
EM 9008
AB [Ac-D2Nal1,4Cl-DPhe2,D3Pal3,Arg5,DGlu6)anisole adduct),DAla10] **gonadotropin**-releasing hormone (Nal-Glu) is an **antagonist** of **LH-RH** and has the potential to be utilized as an antigonadal agent. A study was undertaken to evaluate the toxicol. effects of Nal-Glu in rats. Nal-Glu, dissolved in 5% mannitol in water contg. 9 mL/L benzyl alc., was **administered** s.c. In subchronic studies, groups of male and female rats received 0, 50, 250, or 1250 mug/kg body wt. (BW) Nal-Glu for 90 days and were killed on day 91. Addnl. groups of male and female rats were given the high dose of Nal-Glu (1250 mug/kg BW) or vehicle for either 30 or 90 days. Their **fertility** was assessed by mating them with normal animals. Unlike some other **LH-RH antagonists**, Nal-Glu exhibited a low potency for causing in vitro histamine release from rat peritoneal mast cells. Furthermore, in acute in vivo studies, Nal-Glu was less active in the induction of peripheral edema. In the subchronic study, all doses of Nal-Glu were well tolerated and there were no apparent systematic toxic effects. The pharmacol. effects of Nal-Glu were quite evident, however. Nal-Glu treatment led to a significantly decreased body wt. gain in the males and a significantly increased body wt. gain in the females. There was a dose-dependent decrease in wts. of gonads and **reproductive** organs in both the sexes. Some of the hematol. and serol. parameters were significantly different in Nal-Glu-treated animals. However, most of the values were within the normal range and are considered to be of no toxicol. significance. Histopathol. evaluations were made in the control and high-dose groups only. In the male, a seminiferous tubular degeneration and atrophy of the interstitial cells was seen. The prostate and seminal vesicles were also atrophied and the epididymides were devoid of spermatozoa. In the females, the **ovaries** and uteri were atrophic. The injection site of Nal-Glu-treated rats had inflammatory changes indicative of a local irritating action of the drug. All other tissues had normal histomorphol. Both male and female rats became **infertile** when 1250 mug/kg Nal-Glu was **administered** for 30 days. Normal **fertility** was restored 8 wk after cessation of 90-day treatment. It is concluded that repeated **administration** of Nal-Glu leads to reversible **infertility** in both male and female rats. Although it was irritating at the site of injection, Nal-Glu had no systematic toxicol. effects.

L131 ANSWER 18 OF 47 TOXLIT
AN 90:94246 TOXLIT
DN CA-113-185050J
TI Effects of a luteinizing hormone-releasing hormone antagonist in late-juvenile female rats: blockade of follicle growth and delay of first ovulation following suppression of gonadotropin concentrations.
AU Meijs-Roelofs HM A; Kramer P; Van Cappellen WA; Van Leeuwen EC M
CS Med. Fac., Erasmus Univ., Rotterdam
SO Biol. Reprod, (1990). Vol. 43, No. 4, pp. 607-13.
CODEN: BIREBV. ISSN. 0006-3363.
CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 113:185050
EM 9012
AB S.c. injections of an **antagonist** against **LH-releasing hormone** (LHRH-A, Org. 30276) were **administered** to late-juvenile female rats. The effects were studied on: timing of vaginal opening, 1st **ovulation**, serum **gonadotropin** concns., and follicle growth. d. The dose of 100 mug LHRH-A/100 g, given on days 28, 31, and 34, did not influence timing of 1st **ovulation**. After **administration** of 500 mug LHRH-A/100 g, **ovulation** was retarded by 4.7 days if injections were given on days 28 and 31; by 6.7 days if given on days 28, 31, and 34; and by 11.5 days if given on days 28, 31, 34, and 37. Serum LH and FSH concns. 3 days after the 1st, 2nd, and 3rd injections of 500 mug LHRH-A were lower than in saline-treated controls. **Ovarian** follicle counts showed decreased nos. of (antral) Class 2, 3, and 4 follicles 3 days after injection of 500 mug LHRH-A/100 g on day 28, a higher no. of Class I follicles and a further decrease in Class 2, 3, and 4 follicles 3 days after the 2nd LHRH-A injection; and total absence of Class 3, 4, and 5 follicles 3 days after the 3rd LHRH-A injection. Six days after the 3rd LHRH-A injection, Class 2 and 4 follicles reappeared in the **ovaries**. A single, low-dose injection of LHRH-A **administered** at 0900 h on the day of 1st proestrus blocked 1st **ovulation** in 3 of 11 rats given 2.5 mug and in all (8/8 and 12/12) rats given 5 and 10 mug; **ovulation** was not blocked with 1 mug LHRH-A (0/6 rats) or saline (0/8 rats). Thus, **administration** of LHRH-A to late-juvenile female rats may delay sexual maturation by a decrease in **gonadotropin** levels, causing arrest of follicle growth at an early antral stage. The dose of LHRH-A needed for acute inhibition of the 1st **ovulatory gonadotropin** surge is only a fraction of that causing chronically lower **gonadotropin** levels and subsequent blockade of follicle growth.

L131 ANSWER 19 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 14
AN 90:136563 BIOSIS
DN BA89:75374
TI INHIBITORY EFFECTS OF TREATMENT WITH AN LHRH ANTAGONIST ON THE OVULATORY CYCLE ARE REDUCED WHEN ADMINISTERED DURING THE LATE FOLLICULAR PHASE.
AU FRASER H M
CS MRC REPRODUCTIVE BIOL. UNIT, CENTRE REPRODUCTIVE BIOL., 37 CHALMERS ST., EDINBURGH EH9 3EW, UK.
SO CONTRACEPTION 41 (1). 1990. 73-84. CODEN: CCPTAY ISSN: 0010-7824
LA English
AB To compare the effects of transitory suppression of pituitary **gonadotropin** secretion by an **LHRH antagonist** at the mid or late follicular phase of the menstrual cycle, adult macaques with normal menstrual cycles were treated with an **LHRH antagonist** [N-Ac-D-Nal(2)1, D-pCl-Phe2,D-Trp3,D-hArg(Et2)6,D-Ala10]LHRH (detirelix) **administered** subcutaneously at a dose of 300 .mu.g/kg, daily for 3 days beginning either during the mid or late follicular phase. In all eight animals treated during the mid follicular phase, serum concentrations of LH and FSH declined and remained suppressed for 4 days. This caused a fall in serum concentrations of estradiol and the

expected **ovulation** failed to occur. During the recovery period a marked rise in serum FSH occurred followed by normal follicular development and **ovulation** 14.8 .+-. 0.6 days after the last injection of antagonist. Of the 9 macaques given the same treatment during the late follicular phase, only in two was the expected rise in serum progesterone prevented. In 4 of the animals a transitory suppression in LH and estradiol was observed but this was followed by a recovery and occurrence of an LH surge and rise in serum progesterone indicating **ovulation** during the course of treatment. In the remaining 3 macaques treatment commenced on the day of the initiation of the LH surge and was associated with a progesterone rise of normal duration but lower than normal magnitude during the early luteal phase. These results show that **LHRH antagonist** treatment causes rapid inhibition of pituitary-**ovarian** function when **administered** up to the mid follicular phase of the cycle and is effective in blocking **ovulation**. The suppressive effects of the antagonist are reduced when **administered** during the late follicular phase. This may be due to decreased dependence of the pituitary **gonadotrope** on LHRH at this time and on decreased dependence of the dominant follicle on the **gonadotropins**.

L131 ANSWER 20 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 15
AN 90:75490 BIOSIS
DN BA89:43316
TI EFFECTS OF LHRH ANTAGONIST ADMINISTRATION TO IMMATURE MALE RATS ON SEXUAL DEVELOPMENT.
AU VAN DEN DUNGEN H M; DIJKSTRA H; HIEHLE M A H; VAN REES G P; SCHOEMAKER J
CS DEP. PHARMACOL., MED. FAC., SYLVIUS LAB., UNIV. LEIDEN, P.O. BOX 9503, 2300 RA LEIDEN, NETH.
SO PHYSIOL BEHAV 46 (5). 1989. 779-786. CODEN: PHBHA4 ISSN: 0031-9384
LA English
AB **Gonadotropin** secretion in immature male rats was inhibited by **administration** of a potent **LHRH antagonist** (**LHRH**-A): from 6 to 15 days of age (early onset/short-term treatment), from 6 to 48 days of age (early onset/long-term treatment) or from 22 to 31 days of age (late onset/short-term treatment). Balano-preputial separation was retarded by 9 or 13 days (short-term treatments) or by about 40 days (long-term treatment). Adult testicular weight was lowered and plasma FSH was increased after early, but not after late onset of LHRH-A treatment. Plasma LH and testosterone levels were not affected by any of the LHRH-A treatments. **Fertility** was diminished after early onset LHRH-A **administration** only. Adult precopulatory and copulatory behavior were severely affected after early onset of LHRH-A treatment. Intensity of precopulatory anogenital inspection was increased. The copulatory pattern was incomplete with absence of ejaculatory behavior during sexual behavior tests. Sexual behavior was not affected after late onset of LHRH-A treatment. Thus, **administration** of LHRH-A to immature male rats delays balano-preputial separation irrespective of the age of onset of LHRH-A treatment. In contrast, effects on adult FSH levels, testicular weight, **fertility** and sexual behavior depend on age and duration of LHRH-A **administration**.

L131 ANSWER 21 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 16
AN 90:46997 BIOSIS
DN BA89:24361
TI DIMINISHED ROLE OF LHRH IN THE CONTROL OF GONADOTROPH MORPHOLOGY AND

FUNCTION IN THE LONG-TERM CASTRATED MALE RAT.
AU ALMEIDA O F X; HASSAN A H S; NIKOLARAKIS K E; MARTIN G B
CS INST. PHARMACOL. TOXICOL. PHARM., LUDWIG-MAXIMILIANS-UNIV., KOENIGINSTRASSE 16, D-8000 MUENCHEN 22, FRG.
SO J ENDOCRINOL 123 (2). 1989. 263-274. CODEN: JOENAK ISSN: 0022-0795
LA English
AB It was found in previous studies that the neurotransmitter control of the secretion of LHRH and LH differs between long-term castrated and **ovariectomized** rats. One interpretation of these data was that there was a reduced 'positive drive' in the male, and the question was raised 'how do the **gonadotrophs** of long-term castrated rats maintain a high level of LH secretion?'. In the present series of experiments, evidence for a reduced dependence of the **gonadotrophs** upon LHRH stimulation is provided. Although sensitivity to native LHRH was not compelely lost in long-term castrated rats, two potent **LHRH antagonists** (D-pyroglu1,D-Phe2,D-Trp3,6)-LHRH and (N-acetyl-3,4-dehydro-Pro,p-fluoro-D-Phe2,D-Trp3,6)-LHRH, were found to inhibit LH secretion in short-term castrated and long-term **ovariectomized** rats, but not in long-term castrated rats. Neither blockade of axonal transport with colchicine nor immunoneutralization of LHRH with an antiserum against LHRH (both **administered** 48 h before blood sampling) produced reductions in serum concentrations of LH in long-term castrated rats, although these treatments significantly suppressed LH levels in short-term castrated animals. Chronic (6-day) infusions of the second **LHRH antagonist** (up to 450 .mu.g/day) neither reduced LH secretion nor altered the morphology of the 'castration cells' in the pituitaries of long-term castrated rats. Chronic treatment with testosterone (15 days), however, reversed these parameters to some extent, and when the testosterone treatment was coupled with chronic infusions of the **LHRH antagonist**, significantly lower serum levels of LH and reductions in the size of the castration cells were observed. These data thus indicate that castration cells may function autonomously, without the need for LHRH, and that testosterone in some way restores the dependency on LHRH and/or the responsiveness to LHRH of these cells.

L131 ANSWER 22 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 17
AN 89:318315 BIOSIS
DN BA88:32045
TI IMMUNOREACTIVE INHIBIN CONCENTRATIONS IN SERUM THROUGHOUT THE MENSTRUAL CYCLE OF THE MACAQUE SUPPRESSION OF INHIBIN DURING THE LUTEAL PHASE AFTER TREATMENT WITH A LHRH ANTAGONIST.
AU FRASER H M; ROBERTSON D M; DE KRETSER D M
CS MRC REPROD. BIOL. UNIT, CENT. REPROD. BIOL., 37 CHALMERS ST., EDINBURGH EH3 9EW.
SO J ENDOCRINOL 121 (1). 1989. R9-R12. CODEN: JOENAK ISSN: 0022-0795
LA English
AB Concentrations of immunoreactive inhibin in serum samples collected daily from six adult stumptailed female macaques during normal menstural cycles were measured with an heterologous radioimmunoassay. Serum inhibin concentrations were low during the follicular phase of the cycle. After **ovulation** they began to rise, reaching a plateau between 8 and 11 days, before falling in parallel with the decline in luteal progesterone secretion. The dependence of the inhibin secretion by the corpus luteum on pituitary **gonadotrophins** was investigated by the **administration** of an **LHRH antagonist** [N-Ac-D-Nal(2)1,D-pCl-

Phe2,D-Trp3,D-hArg(Et2)6,D-Ala10]LHRH once daily for 3 days beginning on day 8 of the luteal phase in six macaques. **LHRH antagonist** treatment markedly suppressed serum levels of inhibin and progesterone and these remained at the level found in the follicular phase for the remainder of the luteal phase. These results show that inhibin in the macaque is secreted into the peripheral blood almost exclusively during the luteal phase, being highest when FSH is at its nadir. Suppression of serum inhibin concentrations during the luteal phase by **LHRH antagonist** suggests that its secretion is integrated with the LH control of the corpus luteum.

L131 ANSWER 23 OF 47 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 89105057 EMBASE
TI Immunoreactive inhibin concentrations in serum throughout the menstrual cycle of the macaque: Suppression of inhibin during the luteal phase after treatment with an LHRH antagonist.
AU Fraser H.M.; Robertson D.M.; De Kretser D.M.
CS MRC Reproductive Biology Unit, Centre for Reproductive Biology, Edinburgh EH3 9EW, United Kingdom
SO J. ENDOCRINOL., (1989) 121/1 (R9-R12).
ISSN: 0022-0795 CODEN: JOENAK
CY United Kingdom
DT Journal
FS 003 Endocrinology
030 Pharmacology
LA English
AB Concentrations of immunoreactive inhibin in serum samples collected daily from six adult stumptailed female macaques during normal menstrual cycles were measured with a heterologous radioimmunonassay. Serum inhibin concentrations were low during the follicular phase of the cycle. After **ovulation** they began to rise, reaching a plateau between 8 and 11 days, before falling in parallel with the decline in luteal progesterone secretion. The dependence of the inhibin secretion by the corpus luteum on pituitary **gonadotrophins** was investigated by the **administration** of an **LHRH antagonist** [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Trp3,D-hArg(Et2)6,D-Ala10]LHRH once daily for 3 days beginning on day 8 of the luteal phase in six macaques. **LHRH antagonist** treatment markedly suppressed serum levels of inhibin and progesterone and these remained at the level found in the follicular phase for the remainder of the luteal phase. These results show that inhibin in the macaque is secreted into the peripheral blood almost exclusively during the luteal phase, being highest when FSH is at its nadir. Suppression of serum inhibin concentrations during the luteal phase by **LHRH antagonist** suggests that its secretion is integrated with the LH control of the corpus luteum.

L131 ANSWER 24 OF 47 TOXLIT
AN 90:2368 TOXLIT
DN CA-111-209413S
TI Diminished role of LH-RH in the control of gonadotroph morphology and function in the long-term castrated male rat.
AU Almeida OF X; Hassan AH S; Nikolarakis KE; Martin GB
CS Inst. Pharmacol. Toxicol. Pharm., Ludwig-Maximilians-Univ., Munich
SO J. Endocrinol, (1989). Vol. 123, No. 2, 263-73, 1 plate.
CODEN: JOENAK. ISSN. 0022-0795.
CY Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)

FS CA
LA English
OS CA 111:209413
EM 9001
AB Previous studies showed that the neurotransmitter control of the secretion of LH-RH and LH differs between long-term castrated and **ovariectomized** rats. Thus, it was examd. how **gonadotrophs** of long-term castrated rats maintain a high level of LH secretion. Evidence for a reduced dependence of the **gonadotrophs** upon LH-RH stimulation is provided. Although sensitivity to native LH-RH was not completely lost in long-term castrated rats, 2 potent **LH-RH antagonists** (D-pyroglu1,D-Phe2,D-Trp3,6)-LH-RH and (N-acetyl-3,4-dehydro-Pro,p-fluoro-D-Phe2,D-Trp3,6)-LH-RH, inhibited LH secretion in short-term castrated and long-term **ovariectomized** rats, but not in long-term castrated rats. Neither blockade of axonal transport with colchicine nor immunoneutralization of LH-RH with an antiserum against LH-RH (both **administered** 48 h before blood sampling) produced redns. in serum concns. of LH in long-term castrated rats, although these treatments suppressed LH levels in short-term castrated animals. Chronic (6-day) infusions of the 2nd **LH-RH antagonist** (up to 450 mug/day) neither reduced LH secretion nor altered the morphol. of the castration cells in the pituitaries of long-term castrated rats. Chronic treatment with testosterone (15 days), however, reversed these parameters to some extent, and when the testosterone treatment was coupled with chronic infusions of the **LH-RH antagonist**, lower serum levels of LH and redns. in the size of the castration cells were obsd. Thus, castration cells may function autonomously, without the need for LH-RH, and testosterone in some way restores the dependency on LH-RH and(or) the responsiveness to LH-RH of these cells.

L131 ANSWER 25 OF 47 MEDLINE DUPLICATE 18
AN 89168946 MEDLINE
TI LHRH analogues: their clinical physiology and delivery systems.
AU Fraser H M
SO BAILLIERES CLINICAL OBSTETRICS AND GYNAECOLOGY, (1988 Sep) 2 (3) 639-58. Ref: 67
Journal code: DFO. ISSN: 0950-3552.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 8907
AB LHRH, produced in the hypothalamus from a precursor molecule, forms an essential link between the central nervous system and the anterior pituitary gland and the control of **reproduction**. It is secreted in a pulsatile manner and in patients who lack the hormone it is necessary to replace LHRH in a near-physiological mode. Chronic exposure of the pituitary **gonadotrophes** to LHRH by infusion and to LHRH agonists leads to suppression of pituitary-gonadal function by mechanisms which involve: 1. The over-riding of pulsatile **gonadotrophin** release; 2. Desensitization of the **gonadotrophe**, particularly at the post-receptor level; 3. Inducing production of altered forms of **gonadotrophin** with reduced biological activity. An effective and reversible suppression of pituitary-**ovarian** function

can be readily obtained by **administering** LHRH agonists by nasal spray or by slow-release depot formulations lasting 1-3 months. LHRH agonist therapy is without serious side-effects but more work is required to evaluate the role of oestrogen in maintaining bone density. Suppression of the **gonadotrophe** can also be obtained by the more conventional approach of receptor blockade by **LHRH antagonists**. These have the advantage of causing immediate pituitary suppression but higher doses are required than for agonists. **LHRH antagonists** suitable for clinical evaluation have only recently become available.

L131 ANSWER 26 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 19
AN 87:419771 BIOSIS
DN BA84:86433
TI SUPPRESSION OF LUTEAL FUNCTION BY A LHRH ANTAGONIST DURING THE EARLY LUTEAL PHASE IN THE STUMPTAILED MACAQUE MONKEY AND THE EFFECTS OF SUBSEQUENT ADMINISTRATION OF HUMAN CHORIONIC GONADOTROPIN.
AU FRASER H M; NESTOR J J JR; VICKERY B H
CS MRC REPRODUCTIVE BIOL. UNIT, 37 CHALMERS ST., EDINBURGH EH3 9EW, UK.
SO ENDOCRINOLOGY 121 (2). 1987. 612-618. CODEN: ENDOAO ISSN: 0013-7227
LA English
AB In previous studies a single sc injection of the **LHRH antagonist** [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Trp3,D-hArg(Et2)6,D-Ala10]LHRH during the luteal phase of the stump-tailed macaque menstrual cycle caused a transient suppression of serum LH and progesterone concentrations. To investigate whether a more prolonged suppression of LH release during the early luteal phase could result in a sustained suppression of progesterone, 10 monkeys were treated with 3 consecutive daily injections of 300 .mu.g **LHRH antagonist**/kg beginning on days 0 (n = 2), 1 (n = 1), 3 (n = 2), 4 (n = 2), and 5 (n = 2) after the LH surge. When the antagonist was **administered** on the day of the LH surge, serum concentrations of bioactive LH were still elevated on the following day, but then fell to low levels. Serum progesterone concentrations were subnormal in these monkeys for the next 10 days, but reocvered toward the late luteal phase. In the 8 monkeys receiving antagonist starting between days 1-5 after the LH surge, serum concentrations of bioactive LH were suppressed to near the detection limit of the assay for 4 days after the first injection. Seven of the 8 monkeys demonstrated a progressive decline in serum progesterone concentrations to undetectable values which remained for the duration of the luteal phase. In the remaining monkey the decline in progesterone was less marked; this animal presented a normal progesterone profile 3 days after the last antagonist injection. Premature menses occurred in all 8 monkeys; the next **ovulation** occurred 18.9 .+-. 0.3 days after the last antagonist injection. To test luteal function after antagonist treatment during the early luteal phase and to mimic the rescue of the corpus luteum during a **fertile** cycle and assess the contraceptive effects of antagonist, hCG in daily doses of 30, 60, 90, 180, and 360 IU was **administered** starting on day 7 of the luteal phase to monkeys previously treated with three daily injections of 300 .mu.g antagonist/kg during the early luteal phase. Control monkeys received hCG injections alone. In the controls, hCG **administration** elevated serum progesterone concentrations to 15-20 ng/ml. In three monkeys in which antagonist **administration** did not commence until day 5 or 6, hCG overcame the suppressive effect of the antagonist. However, in seven monkeys in which antagonist **administration** began on days

1-4, hCG caused only a small progesterone rise (maximal range, 1.8-4.9 ng/ml), about 20% of that observed in control monkeys receiving hCG. These results show that the macaque corpus luteum is dependent upon **gonadotropin** support during the early luteal phase. Recovery of pituitary function after 3-day **LHRH antagonist administration** fails to restore luteal progesterone secretion, and the ability of subsequent **administration** of hCG to rescue the corpus luteum is impaired.

L131 ANSWER 27 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 20
AN 87:228801 BIOSIS
DN BA83:116971
TI INHIBITION OF FIRST OVULATION ADMINISTRATION OF AN LHRH ANTAGONIST TO IMMATURE FEMALE RATS.
AU MEIJS-ROELOFS H M A; KRAMER P; VAN CAPPELLEN W A; SCHUILING G A
CS DEP. ANATOMY, MED. FAC., ERASMUS UNIV., P.O. BOX 1738, 3000 DR ROTTERDAM, NETHERLANDS.
SO J ENDOCRINOL 112 (3). 1987. 407-416. CODEN: JOENAK ISSN: 0022-0795
LA English
AB Subcutaneous injections of an **LHRH antagonist** (ALHRH; Org.30093) were **administered** to immature female rats. Neither a single high dose (50 .mu.g) nor repeated daily doses of 5-30 .mu.g ALHRH/day, **administered** between 28 and 38 days of age, influenced the age and body weight at the time of vaginal opening or first **ovulation**. If repeated daily doses of 2 .times. 10 .mu.g ALHRH were given from 32 to 42 or from 37 to 47 days of age, first **ovulation** was delayed by 3.0 and 6.3 days respectively. **Administration** of 10 .mu.g ALHRH at 09.00 h and again at 17.00 h on the day of first pro-oestrus was found to be sufficient to block the expected first **ovulation** in 36 out of 38 rats. This effect could be repeated by **administering** the same doses of ALHRH at pro-oestrus and again on the next day: **ovulation** was blocked in eight out of eight rats. A single dose of 10 .mu.g ALHRH, **administered** on the morning of pro-oestrus, blocked **ovulation** in five out of twelve rats. Both the preovulatory LH and FSH surge, as measured at 16.00 h on pro-oestrus, were found to be inhibited by ALHRH treatment. On the day after pro-oestrus no recruitment of new small antral follicles had occurred in rats with **ovulatory** blockade. Delayed **ovulation** took place 2-5 days after ALHRH injection at pro-oestrus; until 3 days after injection rats were able to **ovulate** their original preovulatory follicles, thereafter newly developed follicles **ovulated** and large **ovarian** cysts were found in the **ovaries**, next to fresh corpora lutea. Chronic **administration** of two injections daily of 10 .mu.g ALHRH from 34 days of age until the morning of first pro-oestrus had marginal effects on the timing of first pro-oestrus and on follicle dynamics. It was concluded that with the ALHRH compound used, and in chronic as well as in acute experiments, first **ovulation** could only be delayed by its **administration** on the day of first pro-oestrus and that the effect was due to acute inhibition of the preovulatory **gonadotrophin** surge.

L131 ANSWER 28 OF 47 TOXLIT
AN 87:30508 TOXLIT
DN CA-106-096351W
TI Suppression of spermatogenesis in a nonhuman primate (Macaca fascicularis) by concomitant gonadotropin-releasing hormone

antagonist and testosterone treatment.
AU Weinbauer GF; Surmann FJ; Nieschlag E
CS Dep. Exp. Endocrinol., Univ. Women's Hosp., Muenster
SO Acta Endocrinol. (Copenhagen), (1987). Vol. 114, No. 1, pp. 138-46.
CODEN: ACENA7. ISSN. 0001-5598.
CY Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 106:96351
EM 8704
AB The effects of concomitant testosterone (T) [58-22-0] supplementation on **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] **antagonist**-induced testicular regression in cynomolgus monkeys (M. fascicularis) were investigated. Four adult monkeys were infused via osmotic minipumps with daily amts. of 2 mg of a potent GnRH antagonist, RS-68439 [89662-30-6], for a period of 104 days. Androgen substitution was provided via T-filled silastic capsules implanted at initiation of GnRH antagonist treatment. Within 1-4 days of GnRH antagonist **administration**, serum concns. of bioactive LH [9002-67-9] became undetectable. The implants maintained serum T at 50-80% of pretreatment levels. Sperm prodn. decreased in 3 out of 4 monkeys. One animal became azoospermic by the 13th week of treatment, and the ejaculates of 2 other monkeys contained <5 .times. 106 sperm. Testicular histol., judging from biopsies at termination of GnRH antagonist treatment, was typical of the hypogonadotropic status in 3 of the 4 monkeys. The most affected tubules contained only spermatogonia and Sertoli cells. Although comparison with GnRH antagonist treatment alone in a previous study indicated a delay of spermatogenic inhibition with testosterone, the potential of GnRH antagonist for male **fertility** regulation was confirmed.

L131 ANSWER 29 OF 47 TOXLIT
AN 88:74909 TOXLIT
DN CA-109-067208M
TI Neonatal treatment with a LH-RH-antagonist: effects on pubertal development in female and male rats.
AU Van den Dungen HM; Van Rees GP; Meijs-Roelofs HM A; Kramer P; Tilders FJ H; Schoemaker J
CS Dep. Gynecol. Obstet., Vrije Univ., Amsterdam
SO Int. Congr. Ser. - Excerpta Med, (1987). Vol. 751, Neuro-Endocrinol. Reprod., pp. 75-84.
CODEN: EXMDA4. ISSN. 0531-5131.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 109:67208
EM 8810
AB To establish the importance of early **gonadotropin** secretion in vivo for the normal development of puberty, this development was studied in male and female rats that had been chronically treated with an **antagonist** to **LH-RH** (ORG. 30276). **Administration** of the **LH-RH antagonist** resulted in a chronic significant suppression of the plasma FSH levels on days 6-21 in the female and up to day 18 in the male rat. The LH levels in the treated female and male rats were suppressed significantly up to about day 18 and from then on remained in the control range until day 120. From day

24 on the plasma FSH levels of the females in the antagonist-treated and control group did not differ at any age to day 120. In the control male rat the normal prepubertal FSH rise was seen from 24 days of age onwards. The antagonist-treated males, however, showed a significantly steeper elevation from day 24 onwards that progressed gradually to about twice the control levels on day 35. These high FSH levels persisted into adulthood (120 days of age), when they were still elevated by .apprx.50%. The wt. of the uteri and **ovaries** were reduced in the treated group and the vaginal opening developed abnormally. The wts. of testes from the **LH-RH antagonist**-treated group were significantly lower than controls. The tubular diam. in the testis was also significantly reduced by ORG. 30276. Whether the effects on pubertal development of treatment of neonatal rats with ORG. 30276 are mediated by the suppression of FSH and(or) LH, or by a direct effect on the gonads, or even via LH-RH itself needs to be further investigated.

L131 ANSWER 30 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 21
AN 86:416233 BIOSIS
DN BA82:91767
TI DIFFERENT NEUROENDOCRINE MECHANISMS REGULATE THE ACUTE PITUITARY FSH RESPONSE TO ORCHIECTOMY AND OVARIECTOMY.
AU BERARDO P V; DEPAOLO L V
CS DEP. PHYSIOLOGY, UNIV. TEXAS HEALTH SCI. CENTER, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TX 78284, USA.
SO NEUROENDOCRINOLOGY 43 (4). 1986. 511-518. CODEN: NUNDAJ ISSN: 0028-3835
LA English
AB The following experiments were conducted to determine whether a sex difference exists in neuroendocrine mechanisms controlling acute pituitary follicle-stimulating hormone (FSH) responses to castration. Adult male rats and 4-day cycling female rats on diestrus 1 were injected intraperitoneally with either phenobarbital sodium (PhB, 80 mg/kg b.w.) or vehicle at 08.00 h. Following a blood collection at 10.00 h, rats given PhB or vehicle were either sham castrated or castrated under ether. Additional blood samples were obtained, and supplemental PhB or vehicle injections were given at 3, 8, 13, 18, and 24 h after castration. **Administration** of PhB to male rats completely prevented acute increases in plasma luteinizing hormone (LH) and FSH levels after orchidectomy (ORDX). In contrast, PhB treatment did not prevent initial rises in plasma FSH levels at 8 hr **ovariectomy** (ORDX). In contrast, PhB treatment did not prevent initial rises in plasma FSH levels between 13 and 24 h. Plasma LH levels were not elevated by 24 h after OVX. In order to specifically evaluate the role of LH-releasing hormone (LHRH) in mediating the PhB-sensitive rises in **gonadotropins** after castration, groups of male rats and female rats on estrus were injected subcutaneously with 400 .mu.g of a potent **LH-RH antagonist** (ALHRH) or oil at 12.00 h. At 10.00 h on the next morning, an initial blood sample was taken, and all rats were castrated under ether. Additional blood samples were taken at times indicated in the previous experiment. Similar to PhB, ALHRH completely abolished ORDX-induced increases in circulating LH and FSH levels. In contrast to PhB, ALHRH partially suppressed increases in plasma FSH levels 8 h after OVX. Similar to PhB, however, ALHRH patially suppressed FSH levels between 13 and 24 h. In a final experiment, FSH release was observed to be episodic 20-24 h after either ORDX or OVX, but not 8-12 h after OVX. Taken together, these results clearly demonstrate that acute increases in nonepisodic FSH

secretion after ORDX are totally mediated by LHRH. In contrast, acute increases in the nonepisodic component of FSH secretion after OVX are due to both an LHRH-dependent and LHRH-independent mechanism (i.e., increase in basal FSH secretion). Finally, in view of the LHRH-independent control of pulsatile FSH release, the present result suggest that central mechanisms regulating episodic discharges of FSH become activated between 13 and 24 h after OVX.

L131 ANSWER 31 OF 47 TOXLIT
AN 86:46379 TOXLIT
DN CA-104-162174C
TI Inhibition of estradiol-induced gonadotropin release in ovariectomized rhesus macaques by a gonadotropin-releasing hormone antagonist.
AU Norman RL; Rivier J; Vale W; Spies HG
CS Health Sci. Cent., Texas Tech Univ., Lubbock
SO Fertil. Steril, (1986). Vol. 45, No. 2, pp. 288-91.
CODEN: FESTAS. ISSN. 0015-0282.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 104:162174
EM 8606
AB Adult **ovariectomized** rhesus macaques were given the **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] **antagonist** [Ac-beta-(2)-D-naphthalenyl-D-Ala1, p-fluoro-D-Phe2,D-Trp3,D-Arg6]-GnRH, by i.v. infusion for 3-3.5 days to det. whether the pos. feedback action of estradiol (E2) [50-28-2] on pituitary LH [9002-67-9] secretion could be inhibited by blockage of GnRH binding to pituitary **gonadotropes**. The LH release was suppressed when the antagonist was given either as a bolus injection every 6 h or as a const. infusion, beginning 24 h after the E2 was **administered**. Both LH release and FSH [9002-68-0] release were suppressed if the GnRH antagonist infusion began when the E2 was **administered**. Thus continued hypothalamic GnRH stimulation of the pituitary is necessary for the full expression of the preovulatory-like **gonadotropin** surge that occurs in **ovariectomized** macaques in response to E2.

L131 ANSWER 32 OF 47 TOXLIT
AN 86:55895 TOXLIT
DN CA-104-219512T
TI The role of catecholamines in the regulation of an induced wave of gonadotropins in ovariectomized rats.
AU Bukiya NG; Babichev VN; Adamskaya EI
CS Lab. Fiziol. Endokrin. Sist., Inst. Eksp. Endokrinol. Klrim. Gormon., Moscow
SO Probl. Endokrinol, (1986). Vol. 32, No. 2, pp. 47-51.
CODEN: PROEAS. ISSN. 0375-9660.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA Russian
OS CA 104:219512
EM 8607
AB The effects of various catecholamine agonists and **antagonists** on **LH-RH** [**9034-40-6**] levels in the preoptic area, arcuate nucleus, and median eminence

and on induced surges of FSH [9002-68-0] and LH [9002-67-9] secretion were studied in **ovariectomized** rats. Alpha-Adrenergic blockade (phentolamine or prazosin) inhibited induced **gonadotropin** release. The **gonadotropin** surge response was recovered when the alpha-adrenergic agonist mesaton was **administered** to previously blocked animals. Dopaminergic agonists (apomorphine) had no effect on the **gonadotropin** surge in adrenoceptor blocked rats. Changes in hypothalamic LH-RH levels during the **gonadotropin** surge and during its blockade and restoration by pharmacol. agents indicated that catecholamines were involved in both the metabolic processes and transport of this neuropeptide. Thus, central catecholaminergic regulation of the **gonadotropin** surge is due primarily to its effect on hypothalamic LH-RH.

L131 ANSWER 33 OF 47 MEDLINE DUPLICATE 22
AN 86141517 MEDLINE
TI [Induction of ovulation in 1985].
L'induction de l'ovulation en 1985.
AU Buvat J; Buvat-Herbaut M
SO JOURNAL DE GYNECOLOGIE, OBSTETRIQUE ET BIOLOGIE DE LA REPRODUCTION, (1985) 14 (7) 899-913. Ref: 85
Journal code: IAZ. ISSN: 0368-2315.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA French
FS Priority Journals
EM 8606
AB There are many methods that can be used to induce **ovulation** when there is a fault in **ovulation** in patients who have normal prolactin levels. These are: Bringing the weight to a normal level. Giving Clomiphene. Giving Tamoxifen. Giving cyclofenil and bromocriptine, which really have no more effect than giving a placebo. Giving **gonadotrophins** in a classical way. This is very useful where there is hypogonadic amenorrhoea but much less useful when the failure of **ovulation** occurs with normal gonadic function. It is accompanied by a risk of multiple pregnancies and of hyperstimulation, which should be monitored by ultrasound very strictly so that it cannot become too serious. The use of purified FSH which theoretically should be more adequate, at least in cases where the gonadic function is normal in spite of failure of **ovulation**. Pulsatile **administration** of LHRH, which in cases of hypothalamic amenorrhoea carries less total risk than giving **gonadotrophins**. Finally, wedge resection of the **ovaries** which is reversed for polycystic **ovaries** that are larger than normal in size, and allied methods. The first choice for hypogonadic hypothalamic amenorrhoea would seem to be the LHRH pump; and for failure of **ovulation** with normal gonadic function Clomiphene or Tamoxifen. When anti-oestrogens fail to correct these latter cases one can choose according to the case between **gonadotrophins**, choosing if possible pure FSH, and/or wedge resection. In the last resort in these cases the LHRH pump can be used. The frequent failure of these methods show that perhaps it is possible to create a hypogonadotrophic hypogonadism by giving agonists for a long time or **antagonists** to **LHRH** in such a way that a second attempt can be made to induce **ovulation** using **gonadotrophins** in better conditions of efficacy and safety.

L131 ANSWER 34 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 23
AN 86:174883 BIOSIS
DN BA81:85299
TI EFFECT OF AN ANTAGONISTIC ANALOG OF LHRH ON HALOPERIDOL-INDUCED HYPERPROLACTINEMIA IN FEMALE RATS.
AU DEBELJUK L; TORRES-ALEMAN I; SCHALLY A V
CS VETERANS ADM. MED. CENT., RES. DEP., NEW ORLEANS, LA. 70146.
SO PEPTIDES (FAYETTEVILLE) 6 (3). 1985. 463-466. CODEN: PPTDD5 ISSN: 0196-9781
LA English
AB The effects of prolonged treatment with the **antagonist** analog of **LHRH** (N-Ac-D-p-Cl-Phe1,2, D-Trp3,D-Arg6,D-Ala10) LHRH (ORG 30276) on the hyperprolactinemia induced by haloperidol were investigated in intact **ovariectomized** female rats. Treatment with ORG 30276 for 20 days significantly reduced prolactin levels elevated by daily injections of haloperidol in intact as well as in **ovariectomized** rats. **Administration** of ORG 30276 also significantly decreased serum LH levels in both types of rats. It is concluded that the **LHRH antagonist** ORG 30276 is able to counteract the hyperprolactinemic effect of haloperidol. This effect might be due to a blockade of the action of endogenous LHRH on the **gonadotrophs**, which results in a suppressing of the paracrine action of these cells on the lactotroph.

L131 ANSWER 35 OF 47 TOXLIT
AN 85:5675 TOXLIT
DN CA-101-222877J
TI Biological activity of a highly potent LH-RH antagonist.
AU McRae GI; Vickery BH; Nestor JJ Jr; Bremner WJ; Badger TM
CS Dep. Physiol., Inst. Biol. Sci., Palo Alto
SO LHRH Its Analogs, (1984). pp. 137-51.
CODEN: 52RGAC.
CY United States
DT Book; (MONOGRAPH)
FS CA
LA English
OS CA 101:222877
EM 8501
AB The biol. activities of RS-29226 (I) [82778-58-3] were examd. in a variety of test systems. I (1.0-16.0 mug) dose-dependently inhibited **ovulation** in rats when **administered** s.c. at noon on the day of diestrus. The propylene glycol/saline vehicle was more efficient than the corn oil vehicle. The requirement for I increased when it was **administered** earlier in the cycle. **Ovulation** was also inhibited by 2 analogs of I and the relative activities were discussed in relation to structure. Continuous superfusion of a pituitary culture system with I (20 ng/mL) inhibited the release of LH [9002-67-9] in response to LH-RH (20 ng/mL). I (500 mug/kg, s.c.) also suppressed LH in castrated rats but had a lesser effect on FSH [9002-68-0] levels. I (80 mug/rat/day) for 14 days abolished the **ovarian** cycle in rats and lower levels resulted in continuous estrus or diestrus. I (200 mug/rat) terminated pregnancy when **administered** on the 10th day. I (1 mg/rat/day, s.c.) for 14 days decreased plasma testosterone [58-22-0] and suppressed **reproductive** organ wt. and spermatogenesis. A single injection of I (100 or 1000 mg/kg, s.c.) also suppressed plasma testosterone and **gonadotropins** in dogs and 5 mg I/kg, s.c. to a male cynomolgus monkey suppressed plasma testosterone for >24 h. The applicability of **LH-RH**

antagonist analogs are briefly discussed in relation to their increased binding affinities and the rapidity and longevity of their suppressive effects on the pituitary and therefore, gonadal function.

L131 ANSWER 36 OF 47 MEDLINE DUPLICATE 24
AN 84144705 MEDLINE
TI [Gonadoliberin. Therapeutic prospects].
Les analogues de la gonadoliberine. Perspectives therapeutiques.
AU Sitruk-Ware R; Le Bouc Y; Gompel A; Mauvais-Jarvis P
SO PRESSE MEDICALE, (1984 Mar 3) 13 (9) 553-8. Ref: 30
Journal code: PMT. ISSN: 0755-4982.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA French
FS Priority Journals; Cancer Journals
EM 8406
AB Since the luteinizing hormone-releasing hormone (LH-RH) has been identified and its mode of action understood, it has become possible to envisage a therapeutic use of long-acting, non toxic analogues. Biochemical modifications of the decapeptide have resulted in the synthesis of potent **LH-RH antagonists** and agonists. Paradoxically, however, the agonists, devised to induce **ovulation**, exert an antagonistic action due to a decrease in the number of pituitary LH-RH receptors and to desensitization of the pituitary gland to the decapeptide. These inhibitory effects are associated with the prolonged activity of the analogues, in contrast with the stimulant effects of physiological LH-RH which has a short half-life and is secreted by bursts. The direct action of LH-RH analogues on gonads suggested by animal experiments has not been found in man since human gonads are devoid of specific LH-RH receptors. Alterations in steroid production are consecutive to the rise in LH initially induced by LH-RH agonists. The complete **gonadotropic** inhibition which follows the **administration** of **LH-RH antagonists** or agonists suggests that these compounds could be used in man, notably for the treatment of hormone-dependent carcinomas and isosexual early puberty and in the field of contraception.

L131 ANSWER 37 OF 47 MEDLINE
AN 85075338 MEDLINE
TI Luteinizing hormone releasing hormone analogues for contraception.
AU Nillius S J
SO CLINICS IN OBSTETRICS AND GYNAECOLOGY, (1984 Dec) 11 (3) 551-72.
Ref: 62
Journal code: DGA. ISSN: 0306-3356.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 8504
AB Peptide contraception based on LH-RH analogues is an interesting, fundamentally new lead to **fertility** control in women and men. A major advantage of using peptides instead of steroids for contraception is the fact that the hypothalamic peptides exert specific actions on the hypothalamic-pituitary-gonadal system and lack systemic effects. They are therefore less likely to cause

metabolic derangements and other generalized adverse effects. **Antagonistic** analogues of **LH-RH** have been synthesized but until recently they have not been potent enough for clinical trials. However, chronic treatment with low doses of superactive stimulatory analogues of LH-RH paradoxically results in desensitization of the pituitary processes responsible for **gonadotrophin** release. This leads to a reversible inhibition of gonadal function. In women, **ovulation** can be inhibited by continuous intranasal LH-RH agonist treatment. In men, higher doses of LH-RH agonists have to be **administered** to suppress the **gonadotrophin** secretion enough to affect spermatogenesis. Optimal **gonadotrophin** suppression is, however, accompanied by a depression of the serum concentration of testosterone with loss of libido and impotence. The superagonists of LH-RH therefore have to be **administered** in combination with testosterone to induce oligo- or azoospermia without impotence. The overall results of clinical trials with superagonists of LH-RH for induction of inadequate corpus luteum function, luteolysis or early abortion in women are not impressive. The contraceptive effectiveness of these approaches to peptide contraception remains to be demonstrated in the human female. Inhibition of normal **ovulation** can, however, be consistently achieved by daily intranasal superagonist **administration** in women. This approach to **fertility** control has already been shown to provide safe and effective contraception in women.

L131 ANSWER 38 OF 47 TOXLIT
AN 84:42112 TOXLIT
DN CA-100-151175V
TI Counteractive effects of agonistic and antagonistic gonadotropin-releasing hormone analogs on spermatogenesis: sites of action.
AU Heber D; Dodson R; Peterson M; Channabasavaiah KC; Stewart JM; Swerdloff RS
CS Dep. Med., Harbor-UCLA Med. Cent., Torrance
SO Fertil. Steril, (1984). Vol. 41, No. 2, pp. 309-13.
CODEN: FESTAS. ISSN. 0015-0282.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 100:151175
EM 8405
AB Both **gonadotropin**-releasing hormone (GnRH) [**9034-40-6**] agonistic and **antagonistic** analogs inhibit **reproductive** hormonal function, but neither class of analog completely inhibited spermatogenesis in man. The potential for a synergistic interaction of submaximal doses of these 2 classes of GnRH analogs was investigated by daily s.c. injections of 200 ng/day of a potent agonist (D-Leu6des-Gly10-GnRH ethylamide [53714-56-0]) and 100 mug/day of a potent antagonist (NAc-L-Ala1,pCl-D-Phe2,D-Trp3,6-GnRH [81557-54-2]), both alone and in combination, to adult male rats for 21 days. Serum **gonadotropins** and testosterone, pituitary GnRH receptor content, gonadal **gonadotropin** receptors, and intratesticular sperm counts were quantitated in each treatment group. Despite the ability of both GnRH agonists and antagonists to inhibit **reproductive** function when **administered** as single agents, combined treatment with the 2 classes of GnRH analogs was less effective than either agent alone at these doses in

the pharmacol. suppression of spermatogenesis.

L131 ANSWER 39 OF 47 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 83-61667K [26] WPIDS
DNC C83-059819
TI Peptides and peptide-resin intermediates - useful as antagonists of luteinising hormone releasing hormone.
DC B04 C03
IN SCHALLY, A V
PA (COYD-I) COY D H
CYC 19
PI EP 81877 A 830622 (8326)* EN 39 pp
R: AT BE CH DE FR GB IT LI LU NL SE
AU 8291025 A 830616 (8331)
FI 8204235 A 830729 (8336)
JP 58126852 A 830728 (8336)
DK 8205498 A 830815 (8339)
ZA 8209041 A 830816 (8348)
HU 27402 T 831028 (8349)
PT 75955 A 840112 (8407)
ES 8406418 A 841101 (8503)
EP 81877 B 860430 (8618) EN
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3270899 G 860605 (8624)
ADT EP 81877 A EP 82-201544 821206
PRAI US 81-329526 811210; US 82-368702 820415
AN 83-61667K [26] WPIDS
AB EP 81877 A UPAB: 930925
Peptides of formula (I) and their salts are new.
X-R1-R2-R3-Ser-Tyr -R4-Leu-Arg-Pro-R5-NH2 (I)
(X is H, 1-6C alkanoyl, HOOC(CH2)nCO or the acyl or N-alkanoylacyl portion of glycine or a D- or L-amino acid; R1 is Gly, L-Ala, L-3-(1-naphthyl)-Ala, L-3-(2-naphthyl)-Ala, D-Ala, D-3-(1-naphthyl)-Ala, D-3-(2-naphthyl)-Ala, D-Trp or D-Phe (opt. ring substd. by halogen, NO2, NH2, 1-4C alkyl, CN, CF3, OH or 1-4C alkoxy); R3 is D-Trp, L-Trp, L-Phe or L- or D-3-(2-naphthyl)-Ala; R4 is D-Lys, D-Arg, D-Orn, D-homo-Arg or D-His; and R5 is Gly or D-Ala).
Peptide-resin intermediates of formula (II) are also new.
X-R1-R2-R3-Ser(R6)-Tyr(R7) -R'4-Leu-Arg(N(G)-R8)-Pro-R5-A (II)
(R'4 is a R4 gp. or N(epsilon)-protected D-Lys, N(delta)-protected D-Orn, N(G)-protected D-Arg, N(G)-protected D-homo-Arg or N(I)-protected His; R6-R8 are H or protective gp.; and A is NH-CH-Ph-Ph-resin or OCH2-Ph-resin).
Cpds. (I) are antagonists of luteinising hormone releasing hormone (LH-RH) with greater potency than prior **LH-RH antagonists**. They are effective on oral **administration**. They are useful for treating conditions associated with the availability of pituitary **gonadotropins**, esp. precocious puberty, hormone dependent tumours, hirsutism, acne, amenorrhoea, endometriosis, and **ovarian** and mammary cystic diseases in man and animals, and for the control of **ovulation**, as pre- and post-coital contraceptives, for synchronising oestrus in livestock, and for regulating human menopausal **gonadotropin**, FSH and LH in women. Dose is 1-1000 micrograms/kg parenterally.
ABEQ EP 81877 B UPAB: 930925
A peptide of formula X-R1-R2-R3-Ser-Tyr-R4-Leu-Arg-Pro-R5-NH2 in which X is hydrogen, lower alkanoyl, or HOOC-(CH2)n-CO wherein n is an integer from 2 to 6, R1 is Gly, L-Ala, L-3-(1-naphtyl)-Ala,

L-3-(2-naphtyl)-Ala, D-Ala, D-3-(1-naphtyl)-Ala, D-3-(2-naphtyl)-Ala, D-Trp, D-Phe or D-Phe having one or more substituents at the phenyl moiety selected from the group consisting of halogen, nitro, amino, alkyl (1-4C), cyano, trifluoromethyl, hydroxy and alkoxy (1-4C); R2 is D-Phe having one or two substituents at the phenyl moiety, one substituent being always in para position which substituent(s) is (are) selected from the group consisting of halogen, nitro, amino, alkyl (1-4C), cyano, trifluoromethyl, hydroxy and alkoxy (1-4C); R3 is D-Trp, L-Trp, L-Phe or L- or D-3-(2-naphtyl)-Ala; R4 is D-Lys, D-Arg, D-Orn, D-homo-Arg or D-His and R5 is Gly or D-Ala; or a therapeutically acceptable salt thereof.

L131 ANSWER 40 OF 47 TOXLIT
AN 84:32503 TOXLIT
DN CA-099-188151W
TI Comparison of the effect of several gonadotropin releasing hormone antagonists on luteinizing hormone secretion, receptor binding and ovulation.
AU Rivier C; Rivier J; Perrin M; Vale W
CS Salk Inst., San Diego
SO Biol. Reprod, (1983). Vol. 29, No. 2, pp. 374-8.
CODEN: BIREBV. ISSN. 0006-3363.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
FS CA
LA English
OS CA 99:188151
EM 8405
AB ADDENDUM Acetyl dehydro3,4-Pro1,p-fluoro-D-Phe2,D-Trp3,6]-LH-RH (I) [78708-43-7], acetyl dehydro3,4-Pro1,p-fluoro-D-Phe2,beta-naphtyl-2-D-Ala3,6]-LH-RH [87687-21-6], and acetyl beta-naphtyl-2-D-Ala1,p-fluoro-D-Phe2,D-Trp3,D-Arg6]-LH-RH (II) [87687-22-7] were highly effective in suppressing LH [9002-67-9] secretion in cultured rat anterior pituitary cells, whereas I was the most effective in preventing the binding of a radiolabeled ligand to receptors of these cells. II, given intragastrically, was the most effective in inhibiting LH secretion in **ovariectomized** rats and to block **ovulation** in intact rats. Although <1% of the intragastric dose of these LH-RH analogs is absorbed, the intragastric **administration** of **LH-RH antagonists** can decrease **gonadotropin** secretion and interfere with **reproductive** function.

L131 ANSWER 41 OF 47 DISSABS COPYRIGHT 1997 UMI Company
AN 81:29015 DISSABS Order Number: AAR8125534
TI DIRECT EFFECTS OF LUTEINIZING HORMONE RELEASING HORMONE (LHRH) ON OVARIAN AND TESTICULAR CELLULAR LH RECEPTORS
AU TALBOT, SUSAN ANN [PH.D.]
CS LOUISIANA STATE UNIVERSITY MEDICAL CENTER IN NEW ORLEANS (0854)
SO Dissertation Abstracts International, (1981) Vol. 42, No. 6B, p. 2298. Order No.: AAR8125534. 122 pages.
DT Dissertation
FS DAI
LA English
AB With the availability of luteinizing hormone releasing hormone (LHRH) analogs, clinicians have attempted to use them to treat **infertility**. However, large doses or chronic **administration** resulted in hypogonadotropic effects.
These hypogonadotropic effects were explained by reduction of

ovarian or testicular LH/hCG receptors, widely held to be due to stimulation of abnormally high concentrations of **gonadotropins**, known as "down regulation".

"Down Regulation" requires an intact pituitary. However, using immature hypophysectomized (hypox) female rats primed with Pregnant Mare's Serum we were able to demonstrate a 97% and a 93% reduction of **ovarian** LH/hCG receptors following injection of 2 (mu)g or 0.2 (mu)g, respectively, of an LHRH analog (D-Trp('6))-LHRH for 7 days, in comparison to saline-injected hypox rats. The **ovarian** weights remained unchanged. Similar reductions of testicular receptors (80% and 60%, respectively) were observed using immature hypox male rats. Analog injections, concomitant with hCG treatment resulted in further reduction of receptors.

The effects of low doses of the potent analog (D-Trp('6))-LHRH were examined. A 1 ng dose of the analog injected s.c. into hypox rats daily for 7 days increased receptor numbers to 485% of saline-injected controls, yet a 200 ng dose reduced testicular LH receptors to 60% of control values. Concomitant injection of the new **LHRH antagonist** Ac D-p-Cl-Phe('1,2)D-Trp('3,6)-LHRH at a dose ratio of 300:1 eliminated both these effects, indicating the LHRH low dose and high dose effects are specific to the LHRH analog. Effects of other pituitary hormones, such as prolactin, were studied using hypox rats with pituitary implants under the kidney capsule. Results suggested that elevations in serum prolactin levels increase LH receptors, but do not prevent the receptor-reducing action of large doses of analog. Also, 7 days treatment with 2 (mu)g analog using hypox, adrenalectomized rats still resulted in an 80% reduction of LH receptors, indicating the receptor-decreasing effect is not mediated by the adrenal.

(Supported by USPHS Grant No. Am-09094 and Veterans **Administration**).

L131 ANSWER 42 OF 47 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 81-77743D [42] WPIDS
TI LH-RH-Antagonist peptide(s) - which can be used to prevent ovulation in mammals.
DC B04
IN RIVIER, J E F; VALE, W W
PA (SALK) SALK INST BIOLOGICAL STUDIES
CYC 2
PI US 4292313 A 810929 (8142)* 5 pp
ZA 8101768 A 820225 (8221)
PRAI US 80-140487 800415; US 80-182594 800829; US 81-256063 810421
AN 81-77743D [42] WPIDS
AB US 4292313 A UPAB: 930915
Peptides of formula (I) and their salts are new:

R1-R2-pCl-D-Phe-D-Trp-Ser -Tyr-R3-R4-Arg-Pro-R5

(R1 is H, formyl, acetyl, acrylyl, benzoyl or allyl; R2 is dehydro-Pro, dehydro-D-Pro, Thz or D-Thz; Thz is meta-thiozolidine-2-carboxylic acid residue; R3 is D-Trp or (imBzl)D-His; R4 is Leu or N(alpha)-Me-Leu; and R5 is Gly- NH2 or NHCH2CH3).

(I) may be prepd. by solid phase techniques, using a chloro-methylated resin for prods. in which R5 is NHCH2CH3 and a benzhydrylamine resin for prods. in which R5 is Gly-NH2. Side- chain protecting gps. are added to the amino acids before they are coupled to the chain being built up into the resin. The intermediate peptido-resin is then treated by ammolysis to cleave the protected peptide from the resin; and/or the resulting peptide or the peptido-resin is deprotected and, if necessary, cleansed using anisole/HF treatment. The prod. may then be purified by

chromatography.
(I) strongly inhibit the secretion of **gonadotrophins** by the pituitary gland of mammals, including humans, and/or inhibit the release of steroids by the gonads of both male and female mammals. In partic., they are **LH-RH antagonists** which inhibit **ovulation** of female mammals when **administered** at very low levels at pro-oestrus, and are also effective to cause resorption of **fertilised** eggs shortly after conception. (I) may be given i.v., s.c., i.m. or p.o. at a dose of 5-20 mg/kg.

L131 ANSWER 43 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 25
AN 82:244315 BIOSIS
DN BA74:16795
TI DIURNAL INFLUENCES ON SERUM LUTEINIZING HORMONE RESPONSES TO OPIATE RECEPTOR BLOCKADE WITH NALOXONE OR TO LHRH IN THE IMMATURE FEMALE RAT.
AU BLANK M S; MANN D R
CS YERKES REGIONAL PRIMATE RES. CENT., EMORY UNIV., ATLANTA, GA. 30322.
SO PROC SOC EXP BIOL MED 168 (3). 1981. 338-343. CODEN: PSEBAA ISSN: 0037-9727
LA English
AB The existence of a temporal pattern was investigated in the **gonadotropin** response of immature rats to **LHRH** or the opiate **antagonist**, naloxone. Thirty-day-old female rats were injected at 3-h intervals over a 24-h period with either naloxone (2.5 mg/kg body wt) or LHRH (8 ng/100 g body wt). Animals were decapitated 15 min later and serum samples were assayed for luteinizing hormone (LH) by radioimmunoassay. The serum LH response to naloxone and LHRH varied significantly with the time of day. Naloxone **administration** had no statistically significant ($P > 0.05$) effect on levels of serum LH at 1500 and 1800 h compared to levels in saline-injected controls, but induced a significant rise in serum LH at all other times. Naloxone had its greatest effect during the late evening and early morning hours (2100-0900 h). A similar, but not identical, pattern of LH responsiveness to LHRH was observed, with the 2 rhythms being truly divergent only during the late afternoon when LH sensitivity to LHRH was high but low to naloxone. There is a diurnal pattern of pituitary sensitivity to both naloxone and LHRH in the immature rat. Temporal variations in the LH response to opiate antagonists may result from altered pituitary sensitivity to endogenous LHRH. However, the enhanced response of the pituitary to LHRH during the late afternoon, when opioid inhibition of hypothalamic LHRH secretion appears to be at a nadir, could provide a mechanism in the immature rat whereby adult-like LH surges can be stimulated. The early afternoon LH response to various doses of naloxone was examined in intact and **ovariectomized** 30-day-old rats. Intacts displayed a lower absolute but higher percentage increase above basal values of LH than did **ovariectomized** animals. These latter findings contrast with those previously found in adult female rats.

L131 ANSWER 44 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 26
AN 81:184925 BIOSIS
DN BA71:54917
TI INHIBITION OF PRE OVULATORY GONADOTROPIN SECRETION IN THE RHESUS MONKEY BY 1 PYRO GLUTAMYL PROLINE 2-D PHENYL ALANINE 3-D TRYPTOPHAN 6-D TRYPTOPHAN LUTEINIZING HORMONE RELEASING HORMONE.
AU WILKS J W; FOLKERS K; BOWERS C Y; HUMPHRIES J; SCHIRCKS B; FRIEBEL K
CS FERTIL. RES., UPJOHN CO., KALAMAZOO, MICH. 49001.

SO CONTRACEPTION 22 (3). 1980. 313-324. CODEN: CCPTAY ISSN: 0010-7824
LA English
AB The 1st example of a complete inhibition of preovulatory **gonadotropin** secretion, resulting from **administration** of a luteinizing hormone releasing hormone [luliberin] antagonist during a spontaneous menstrual cycle, is reported. The antagonist, [(< Glu-Pro)1,D-Phe2,D-Trp3,6]-LHRH, was **administered** to a rhesus monkey beginning on Day 9 of the menstrual cycle; **ovulation** did not occur, and preovulatory peaks of LH [lutropin] and FSH [follitropin] were not observed, despite elevations in serum estradiol-17.beta. of sufficient strength and duration to elicit **gonadotropin** surges. Midcycle **gonadotropin** surges had already commenced in another monkey; however, the antagonist did partially inhibit LH and FSH secretion, although **ovulation** and luteinization were not prevented. Normal hormone secretion patterns and luteal function were observed in another monkey when the antagonist was given, after the midcycle FSH and LH peaks had already occurred. These data emphasize the importance of beginning treatment with **LHRH** **antagonists** early in the follicular phase of the menstrual cycle.

L131 ANSWER 45 OF 47 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.
AN 80080484 EMBASE
TI Luteinizing hormone-releasing hormone suppression of human placental progesterone production.
AU Wilson E.A.; Jawad M.J.
CS Dept. Obstet. Gynecol., Univ. Kentucky Coll. Med., Lexington, Ky. 40536, United States
SO FERTIL. STERIL., (1980) 33/1 (91-93).
CODEN: FESTAS
CY United States
LA English
AB A luteinizing hormone-releasing hormone (LHRH), immunologically and biologically similar to hypothalamic LHRH, has been isolated from human placenta. LHRH has been detected in human placenta after 12 weeks of gestation, and its presence raises the possibility that LHRH modulates placental hormone production. Khodr and Siler-Khodr demonstrated LHRH stimulation of human chorionic **gonadotropin** (hCG) and luteinizing hormone (LH) production by placental tissue in vitro. In other animals, LHRH has demonstrated both agonist and **antagonist** effects during pregnancy. **LHRH** (or its analogs) stimulates pituitary **gonadotropins** which cause **ovarian** and uterine hypertrophy, but LHRH prevents nidation and interrupts pregnancy in the rat, rabbit, and hamster. This dual effect has been attributed to excessive production of LH which may be luteolytic in these animals, resulting in decreased progestational activity. Recently, Koyama et al. observed a decrease in progesterone production following the **administration** of an LHRH analog to postovulatory women. Excessive LH or hCG suppresses **ovarian** **gonadotropin** receptors, which may explain the luteolytic effect of LHRH, but a direct effect of LHRH on progesterone synthesis has not been investigated. The purpose of this study was to examine the effect of LHRH on progesterone production by human placenta in organ culture.

L131 ANSWER 46 OF 47 MEDLINE DUPLICATE 27
AN 79170189 MEDLINE
TI Peptide contraception: antifertility properties of LH-RH analogues.

AU Corbin A; Beattie C W; Jones R; Bex F
SO INTERNATIONAL JOURNAL OF GYNAECOLOGY AND OBSTETRICS, (1979 Mar-Apr) 16 (5) 359-72.
Journal code: E4T. ISSN: 0020-7292.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 7909
AB A prototype **LH-RH antagonist** dampened the proestrous **gonadotropin** surge and blocked **ovulation** but had no effect on pregnant animals. In contrast, LH-RH and two highly potent LH-RH agonists terminated pregnancy when **administrated** prior to or following implantation. This contragestational effect, as well as other antireproductive properties of the agonists, coupled with the reversibility of their effects, strongly suggest that peptides may provide a new basis for contraception.

L131 ANSWER 47 OF 47 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 28
AN 79:144008 BIOSIS
DN BA67:24008
TI EFFECT OF LUTEINIZING HORMONE RELEASING HORMONE PEPTIDE ANTAGONIST ON SERUM LUTEINIZING HORMONE OVULATION AND MENSTRUAL CYCLE OF CRAB-EATING MACAQUE.
AU CORBIN A; JASZCZAK S; PELUSO J; SHANDILYA N L; HAFEZ E S E
CS ENDOCRINOL. SECT., RES. DIV., WYETH LAB. INC., BOX 8299, PHILADELPHIA, PA. 19101, USA.
SO CONTRACEPTION 18 (2). 1978 105-120. CODEN: CCPTAY ISSN: 0010-7824
LA English
AB The effects of the **antagonistic LH-RH** [luteinizing hormone-releasing hormone] analog, D-(PHE2)-D-(ALA6)-LH-RH (Wy-18,185), were studied in the female crab-eating macaque (Macaca fascicularis) with emphasis on length of menstrual cycle, length and intensity of menstrual bleeding, serum LH [luteinizing hormone], quantity and properties of cervical mucus, growth of the follicle and **ovulation** during the treatment and subsequent control cycles. Prior to the expected **ovulation**, the compound was **administered** s.c., 25 mg/kg body wt per day, for 3 or 6 days. Blood was collected daily before, during and after treatment. Cervical mucus characteristics were charted daily. Laparoscopy was performed 2-4 days after presumed **ovulation** . Neither the length of the menstrual cycle nor the quality of the cervical mucus were dramatically altered during treatment with Wy-18,185. Of the 9 macaques that were treated with 6 doses of Wy-18,185, 2 had anovulatory cycles associated with premature LH surges and 1 was devoid of an LH surge. The partial anti-**ovulatory** effect of Wy-18,185 in the monkey may be due to its mildly inherent **gonadotropin** releasing properties triggering an LH surge at a time when the follicles were incapable of a complete **ovulatory** response. The general lack of effect of the antagonist, coupled with reports on the comparative refractoriness to LH-RH and related agonists, on **reproductive** parameters in this primate species, in contrast to the rat, rabbit and hamster, indicate that the macaque may be an inappropriate model.

FILE 'USPATFULL' ENTERED AT 17:01:30 ON 03 SEP 1997

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Aug 1997 (19970826/PD)
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>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
            3 L55
         2205 GONADOTROP?
          285 L56
          490 LHRH
         5848 LH
         1430 LUTEIN?
           97 HORMON
            3 LUTEIN? HORMON
                (LUTEIN?(W)HORMON)
        20970 RH
       535322 RELEAS?
        17410 HORMONE#
           66 GONADORELIN
        16918 ANTAGON?
        23675 FERTIL?
         1025 INFERTIL?
         7427 OVAR?
        60854 REPRODUCT?
          556 REPROD##
         1550 OVULAT?
         2030 GYNECOL?
        97654 ADMIN?
L132       61 L95(L) ADMIN?

=> s l132 and (treat? or therap? or control? or regulat?)
       516481 TREAT?
        71952 THERAP?
      1211279 CONTROL?
       263739 REGULAT?
L133       61 L132 AND (TREAT? OR THERAP? OR CONTROL? OR REGULAT?)

=> s l132(l)(treat? or therap? or control? or regulat?)
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        516481 TREAT?
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       1211279 CONTROL?
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L134         60 L132(L)(TREAT? OR THERAP? OR CONTROL? OR REGULAT?)

=> s l134(l)(method# or technique#)
       1144426 METHOD#
        551984 TECHNIQUE#
L135         60 L134(L)(METHOD# OR TECHNIQUE#)

=> d 1-60 bib abs; fil hom

L135 ANSWER 1 OF 60  USPATFULL
AN      97:56710  USPATFULL
TI      Ovulation control by regulating nitric oxide levels
IN      Garfield, Robert E., Friendswood, TX, United States
        Yallampalli, Chandrasekhar, Houston, TX, United States
PA      Board of Regents, The University of Texas System, Austin, TX,
        United States (U.S. corporation)
PI      US 5643944  970701
AI      US 95-477189  950607 (8)
RLI     Division of Ser. No. US 93-165309, filed on 10 Dec 1993, now
        patented, Pat. No. US 5470847
DT      Utility
EXNAM   Primary Examiner: Criares, Theodore J.
LREP    Arnold White & Durkee
CLMN    Number of Claims: 3
ECL     Exemplary Claim: 1
DRWN    1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 571
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      The stimulation of ovulation in a female may be achieved by
        administering a nitric oxide source, optionally in further
        combination with one or more of clomiphene, a gonadotropin, and an
        LH-RH agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 2 OF 60  USPATFULL
AN      97:52131  USPATFULL
TI      Redox amino acids and peptides containing them
IN      Bodor, Nicholas S., Gainesville, FL, United States
PA      University of Florida, Gainesville, FL, United States (U.S.
        corporation)
PI      US 5639885  970617
AI      US 95-395821  950228 (8)
RLI     Continuation of Ser. No. US 91-766391, filed on 27 Sep 1991, now
        abandoned which is a division of Ser. No. US 89-417037, filed on 4
        Oct 1989, now patented, Pat. No. US 5079366 which is a division of
        Ser. No. US 87-35648, filed on 7 Apr 1987, now patented, Pat. No.
        US 4888427
DT      Utility
EXNAM   Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D.
        Margaret M.
LREP    Burns, Doane, Swecker & Mathis, L.L.P.
CLMN    Number of Claims: 32
ECL     Exemplary Claim: 1
DRWN    No Drawings
LN.CNT 2783
```

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel amino acids and peptides containing them which comprise a dihydropyridine.revreaction.pyridinium salt-type redox system and which provide site-specific and sustained delivery of pharmacologically active peptides to the brain. These new amino acids contain a redox system appended directly or via an alkylene bridge to the carbon atom adjacent to the carboxyl carbon and may be incorporated into a peptide chain at a variety of positions, including non-terminal positions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 3 OF 60 USPATFULL
AN 97:40782 USPATFULL
TI Controlled release systems and low dose androgens
IN Labrie, Fernand, Quebec, Canada
Lepage, Martin, Quebec, Canada
PA Endorecherche Inc., Quebec, Canada (non-U.S. corporation)
PI US 5629303 970513
AI US 95-398096 950303 (8)
RLI Division of Ser. No. US 92-900817, filed on 24 Jun 1992, now patented, Pat. No. US 5434146 which is a continuation-in-part of Ser. No. US 91-724532, filed on 28 Jun 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen, LLP
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment and prevention of estrogen-related diseases, and of fertility control, include low dose (e.g. less than 50 nanomolar serum concentration)administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 4 OF 60 USPATFULL
AN 97:36154 USPATFULL
TI Brain-enhanced delivery of neuroactive peptides by sequential metabolism
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5624894 970429
AI US 95-428488 950427 (8)
RLI Continuation of Ser. No. US 92-946062, filed on 17 Sep 1992, now abandoned
DT Utility
EXNAM Primary Examiner: Lukton, David
LREP Burns, Doane, Swecker & Mathis, L.L.P.
CLMN Number of Claims: 67
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 4149
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel peptide derivatives which are designed to deliver pharmacologically active peptides into the central nervous system by sequential metabolism. The peptide is placed in a molecular environment which disguises its peptide nature and provides biolabile, lipophilic functions to penetrate the blood-brain barrier by passive transport. The design incorporates a dihydropyridine-type redox targetor moiety, an amino acid or di- or -tripeptide spacer inserted between the targetor and N-terminal amino acid unit of the peptide and a bulky, lipophilic substituent protecting the C-terminal amino acid unit of the peptide. The dihydropyridine-type targetor undergoes an enzymatically mediated oxidation to a hydrophilic, membrane-impermeable pyridinium salt. That polar targetor-peptide conjugate is trapped behind the lipoidal blood-brain barrier. Over time, cleavage of the lipophilic ester from the peptide by esterase and or lipase enzymes and enzymatic cleavage of the targetor-spacer from the peptide results in release of the desired peptide in the brain.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 5 OF 60 USPATFULL
AN 96:97032 USPATFULL
TI Methods for preventing and treating osteoporosis with low dose non-masculinizing androgenic compounds
IN Labrie, Fernand, Quebec, Canada
PA Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)
PI US 5567695 961022
AI US 95-483761 950607 (8)
RLI Division of Ser. No. US 94-282964, filed on 29 Jul 1994 which is a division of Ser. No. US 93-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 91-724532, filed on 28 Jun 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen, LLP
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and endometriosis in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 6 OF 60 USPATFULL
AN 96:77760 USPATFULL
TI Combination therapy for the treatment of estrogen-sensitive disease
IN Labrie, Fernand, Quebec, Canada
PA Endorecherche Inc., Quebec, Canada (non-U.S. corporation)
PI US 5550107 960827

AI US 91-785890 911104 (7)
RLI Continuation of Ser. No. US 89-321926, filed on 10 Mar 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Jordan, Kimberly
LREP Ostrolenk, Faber, Gerb & Soffen, LLP
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1665
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treatment of breast and endometrial cancer in susceptible warm-blooded animals may include inhibition of ovarian hormonal secretion by surgical (ovariectomy) or chemical (use of an LHRH agonist, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]LHRH ethylamide or antagonist) as part of a combination therapy comprising administering an antiestrogen together with at least one compound selected from the group consisting of an androgen, a progestin, at least one inhibitor of sex steroid formation, especially 17.beta.-hydroxysteroid dehydrogenase and aromatase activity, at least one inhibitor of prolactin secretion, one inhibitor of growth hormone secretion and one inhibitor of ACTH secretion. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such composition are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 7 OF 60 USPATFULL
AN 96:72882 USPATFULL
TI Activation of androgen receptors with low dose non-masculinizing androgenic compounds
IN Labrie, Fernand, Quebec, Canada
PA Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)
PI US 5545634 960813
AI US 94-282964 940729 (8)
RLI Division of Ser. No. US 93-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 91-724532, filed on 28 Jun 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen, LLP
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1406
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and endometriosis in susceptible warm-blooded animals comprising administering a low dose. Of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 8 OF 60 USPATFULL
AN 96:67992 USPATFULL

TI Controlled release systems and low dose androgens
IN Labrie, Fernand, Quebec, Canada
Lepage, Martin, Quebec, Canada
PA Endorecherche, Inc., Canada (non-U.S. corporation)
PI US 5541172 960730
AI US 95-474347 950607 (8)
RLI Division of Ser. No. US 95-398096, filed on 3 Mar 1995 which is a division of Ser. No. US 92-900817, filed on 24 Jun 1992 which is a continuation-in-part of Ser. No. US 91-724532, filed on 28 Jun 1991
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 13 Drawing Page(s)
LN.CNT 2236
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment and prevention of estrogen-related diseases, and of fertility control, include low dose (e.g. less than 50 nanomolar serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 9 OF 60 USPATFULL
AN 96:67979 USPATFULL
TI Calcitonin derivatives
IN Albert, Rainer, Basel, Switzerland
Bauer, Wilfried, Lampenberg, Switzerland
Cardinaux, Fran.cedilla.ois, Seewen, Switzerland
Pless, Janos, Basel, Switzerland
PA Sandoz Ltd., Basel, Switzerland (non-U.S. corporation)
PI US 5541159 960730
AI US 94-346118 941129 (8)
RLI Continuation of Ser. No. US 93-57066, filed on 3 May 1993, now abandoned which is a continuation of Ser. No. US 92-916284, filed on 17 Jul 1992, now abandoned which is a continuation of Ser. No. US 91-781789, filed on 23 Oct 1991, now abandoned which is a continuation of Ser. No. US 89-334969, filed on 7 Apr 1989, now abandoned
PRAI GB 88-8275 880408
GB 88-8528 880412
DT Utility
EXNAM Primary Examiner: Schain, Howard E.
LREP Honor, Robert S.; Kassenoff, Melvyn M.; McGovern, Thomas O.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1368
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Peptide derivatives selected from (i) a calcitonin peptide and a LHRH antagonist peptide modified by at least one sugar residue and/or at least one short polyhydroxy compound or derivative, and (ii) a calcitonin peptide modified by at least one formyl and/or at least C.sub.3-5 alkyl attached to an amino group other than a N-terminal amino group, and (iii) a calcitonin peptide modified by

a combination of said substituents, with the provisos that

i) when the calcitonin peptide comprises at least one sugar residue a), this sugar residue is attached by a coupling other than a direct N-glycosidic bond to an .omega.-amino group of an .omega.-amino substituted side chain in the 24 position, and

ii) when the LHRH antagonist comprises at least one sugar residue a), this sugar residue is an Amadori sugar residue attached by a coupling other than a direct N-glycosidic bond to an .omega.-amino group of an .omega.-amino substituted side chain in the 8 position

in free form or in salt or complex form, have pharmacological activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 10 OF 60 USPATFULL
AN 96:41325 USPATFULL
TI Luteinizing hormone releasing hormone antagonist peptides
IN Deghenghi, Romano, Chesaux Dessus B1, 1264 St. Cergue, Switzerland
PA Deghenghi, Romano, St. Cergue, Switzerland (non-U.S. individual)
PI US 5516887 960514
WO 9219651 921112
AI US 94-140045 940117 (8)
WO 92-EP572 920317
940117 PCT 371 date
940117 PCT 102(e) date
DT Utility
EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: Prickril, Benet
LREP Pennie & Edmonds
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 403
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A luteinizing hormone releasing hormone antagonist peptide is provided which effectively decreases plasma levels of estrogens and androgens. The peptide exhibits increased levels of potency while at the same time minimizing histamine releasing properties, vascular permeability (or edematogenic effects), hypotension, poor water solubility an inadequate duration of action associated with luteinizing hormone releasing hormone antagonist peptides of the past.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 11 OF 60 USPATFULL
AN 96:41199 USPATFULL
TI LHRH antagonists having lactam groups at the N-terminus
IN Swenson, Rolf E., Grayslake, IL, United States
Haviv, Fortuna, Deerfield, IL, United States
Mort, Nicholas A., Waukegan, IL, United States
PA TAP Holdings Inc., Deerfield, IL, United States (U.S. corporation)
PI US 5516759 960514
AI US 94-352305 941208 (8)
DT Utility
EXNAM Primary Examiner: Russel, Jeffrey E.
LREP Janssen, Jerry F.

CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2707
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Peptides possessing LHRH antagonistic activity, and useful for the controlling the release of LHRH in mammals are decapeptide analogues of LHRH having a lactam group at the N-terminus of the formula ##STR1## where n is 1, 2, or 3 and R.sup.1 is selected from the group consisting of hydrogen, benzyl, 4-chlorobenzyl, 2-methylnaphth-1-yl, 1-methylnaphth-2-yl, and quinolin-3-ylmethyl.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 12 OF 60 USPATFULL
AN 96:38893 USPATFULL
TI Submicron emulsions for delivery of peptides
IN Friedman, Doron, Carmei Yosef, Israel
Schwarz, Joseph, Rehovot, Israel
Amselem, Shimon, Rehovot, Israel
PA Pharmos Corporation, New York, NY, United States (U.S. corporation)
PI US 5514670 960507
AI US 93-106107 930813 (8)
DT Utility
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Prickril, Benet
LREP Pennie & Edmonds
CLMN Number of Claims: 39
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 869
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides emulsions comprising a plurality of submicron particles, a bioactive peptide, and an aqueous continuous phase or that effect enhanced oral bioavailability of the peptide. Another aspect of the invention provides compositions and methods of administering peptides in an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption of the bioactive peptide through mucosal surfaces by achieving mucoadhesion of the emulsion particles. Mucous surfaces suitable for application of the emulsions of the present invention may include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 13 OF 60 USPATFULL
AN 96:31932 USPATFULL
TI Cyclic peptide LHRH antagonists
IN Sauer, Daryl R., Gurnee, IL, United States
Haviv, Fortuna, Deerfield, IL, United States
PA Tap Holdings Inc., Deerfield, IL, United States (U.S. corporation)
PI US 5508383 960416
AI US 94-208544 940309 (8)
DT Utility
EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: Wessendorf, T. D.

LREP Janssen, Jerry F.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1163
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A class of cyclic peptides are effective inhibitors of LHRH and are useful in the treatment of disease conditions which are mediated by sex hormones including prostate cancer, endometriosis, uterine fibroids, and precocious puberty.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 14 OF 60 USPATFULL
AN 96:24922 USPATFULL
TI N-terminus modified analogs of LHRH
IN Haviv, Fortuna, Deerfield, IL, United States
Fitzpatrick, Timothy D., Boulder, CO, United States
Swenson, Rolf E., Grayslake, IL, United States
Nichols, Charles J., Greendale, WI, United States
Mort, Nicholas A., Waukegan, IL, United States
PA Tap Holdings Inc., Abbott Park, IL, United States (U.S. corporation)
PI US 5502035 960326
AI US 94-279677 940727 (8)
RLI Continuation-in-part of Ser. No. US 93-103474, filed on 6 Aug 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Schain, Howard E.
LREP Janssen, Jerry F.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2936
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Decapaptide and undecapaptides substituted on the N-terminal nitrogen atom by acyl groups which include furo-2-yl, isonicotinyl, nicotinyl, 2-, 3-, and 4-quinolinecarbonyl, shikimyl, dihydroshikimyl, and tetrahydrofur-2-oyl are potent antagonists of LHRH and are useful for suppressing the levels of sex hormones in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 15 OF 60 USPATFULL
AN 96:12938 USPATFULL
TI LHRH antagonists having modified aminoacyl residues at positions 5 and 6
IN Haviv, Fortuna, Deerfield, IL, United States
Greer, Jonathan, Chicago, IL, United States
Swenson, Rolf E., Grayslake, IL, United States
Sauer, Daryl R., Gurnee, IL, United States
PA TAP Holding Inc., Abbott Park, IL, United States (U.S. corporation)
PI US 5491217 960213
AI US 94-282411 940728 (8)
RLI Continuation of Ser. No. US 92-993202, filed on 18 Dec 1992, now abandoned
DT Utility
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Prickril,

Benet
LREP Janssen, Jerry F.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1256
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A class of potent LHRH decapeptide antagonists possess N-alkylated aminoacyl residues where the side-chain portion of the residue is a 4-(substimtedamino)phenylalanyl, 4-(substituted-amino)cyclohexylalanyl, or .OMEGA.-(substitutedamino)alkyl group, and additionally the aminoacyl residues at position 5 are N-alkylated on the nitrogen atom of the peptide backbone.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 16 OF 60 USPATFULL
AN 95:105937 USPATFULL
TI CHRH antagonists with low histamine release
IN Folkers, Karl A., Austin, TX, United States
Ljungqvist, Anders, Austin, TX, United States
Feng, Dong-Mei, Austin, TX, United States
Kubota, Minoru, Yotsukaido, Japan
Tang, Pui-Fun L., Hong Kong, Hong Kong
Bowers, Cyril Y., New Orleans, LA, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5470947 951128
AI US 89-371552 890626 (7)
RLI Continuation-in-part of Ser. No. US 87-88431, filed on 24 Aug 1987, now patented, Pat. No. US 4935491, issued on 19 Jun 1990
DT Utility
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Wessendorf, T. D.
LREP Arnold, White & Durkee
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1888
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Antide is the decapeptide, N--Ac--D--2--Nal,D--pClPhe, D--3--Pal, Ser,NicLys, D--NicLys, Leu, ILys, Pro, D--Ala,NH.sub.2 which is an antagonist of luteinizing hormone releasing hormone (LHRH). This decapeptide, like others of the present invention, has high antiovulatory activity (AOA) and releases negligible histamine. Antide is scheduled for scale-up, safety testing and evaluation in the experimental primate and in clinical medicine. Numerous other peptides having structures related to Antide were prepared and tested. These peptides had variations primarily in positions 5, 6, 7, and 8. Of these, N--Ac--D--2--Nal, D--pClPhe,D--3--Pal,Ser,PicLys,cis--DpzACAla, Leu,ILys,pro,D--Ala--NH.sub.2 was one of the most potent and had higher antiovulatory activity than Antide, i.e. 73%/0.25 ug and 100%/0.5 ug vs. 36%/0.5 ug and 100%/1.0 ug. Antide showed significant, ($p<0.001$) duration of action, when injected at a dose of 10 ug, 44 hours before 50 ng of the agonist, [D--3--Qal.sup.6]--LHRH. Antide showed oral AOA at 600 ug (73%) and at 1200 ug (100%) with negligible difference being found between water and corn oil oral formulations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 17 OF 60 USPATFULL
AN 95:105837 USPATFULL
TI Ovulation control by regulating nitric oxide levels with arginine derivatives
IN Garfield, Robert E., Friendswood, TX, United States
Yallampalli, Chandrasekhar, Houston, TX, United States
PA Board of Regents, the University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5470847 951128
AI US 93-165309 931210 (8)
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Arnold, White & Durkee
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 616
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Inhibition of ovulation in a female may be achieved by administering an arginine derivative which acts as a nitric oxide sythase inhibitor, alone or in combination with one or more of a progestin, an estrogen, and an LH-RH antagonist, thereby preventing conception.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 18 OF 60 USPATFULL
AN 95:97033 USPATFULL
TI Methods of inhibiting fertility in women
IN Jones, Charles D., Indianapolis, IN, United States
Tinsley, Frank C., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5462949 951031
AI US 93-170945 931221 (8)
DT Utility
EXNAM Primary Examiner: Fay, Zohreh
LREP Sales, James J.; Dahling, Gerald V.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 385
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of inhibiting fertility in women comprising administering to a female human an effective amount of a compound having the formula ##STR1## and pharmaceutically acceptable salts and solvates thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 19 OF 60 USPATFULL
AN 95:78164 USPATFULL
TI Formulations and method of the percutaneous administration of leuprolide
IN Lu, Mou-Ying Fu, Lake Bluff, IL, United States
Subba Rao, Gowdahallin N., Mundelein, IL, United States
Lee, Dennis Y., Highland Park, IL, United States

PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5446025 950829
AI US 92-897680 920612 (7)
DT Utility
EXNAM Primary Examiner: Hill, Jr., Robert J.; Assistant Examiner: Davenport, A. M.
LREP Janssen, Jerry F.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 437
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions useful for the percutaneous administration of leuprolide comprise from about 1 to about 100 mg/ml of leuprolide in its free base form, a cutaneous membrane penetration enhancing component, and a pharmaceutically acceptable carrier. The cutaneous membrane transport enhancing component comprises from about 1 percent to about 15 percent urea, from 1 percent to about 5 percent menthol, from about 0.5 percent to about 5 percent methyl salicylate, and from about 0.5 percent to about 5 percent camphor, all percentages expressed in weight/volume based upon the total volume of the composition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 20 OF 60 USPATFULL
AN 95:64916 USPATFULL
TI Controlled release systems and low dose androgens
IN Labrie, Fernand, Quebec, Canada
Lepage, Martin, Quebec, Canada
PA Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)
PI US 5434146 950718
AI US 92-900817 920624 (7)
DCD 20111108
RLI Continuation-in-part of Ser. No. US 91-724532, filed on 28 Jun 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2424
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment and prevention of estrogen-related diseases, and of fertility control, include low dose (e.g. less than 50 nanomolaR serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 21 OF 60 USPATFULL
AN 95:64908 USPATFULL
TI Gonadoliberin antagonists
IN Konig, Wolfgang, Hofheim am Taunus, Germany, Federal Republic of
Sandow, Jurgen, Konigstein/Taunus, Germany, Federal Republic of

Kolar, Cenek, Marburg, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5434138 950718
AI US 93-151056 931112 (8)
RLI Continuation of Ser. No. US 91-739233, filed on 1 Aug 1991, now abandoned
PRAI DE 90-40247791 900804
DT Utility
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Marshall, S. G.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 801
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Peptides of the formula ##STR1## in which X is alkanoyl, A is optionally substituted D-Nal(2), D-Phe or D-Trp, B is optionally substituted D-Phe, C is D-Pal(3) or optionally substituted D-Phe or D-Trp, and D is Tyr or His, E is D-Ser (R.sup.1), F is Leu, Trp or Phe, G is L-Ser(R.sup.1), H is Gly-NH.sub.2, D-Ala-NH.sub.2 or Azagly-NH.sub.2 and R.sup.1 is a glycosyl radical. These peptides have an inhibitory effect on the formation of the gonadotropins lutropin and follitropin and thus also on the synthesis of testo-sterone and estrogen. A process for the preparation of these peptides is described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 22 OF 60 USPATFULL
AN 95:49945 USPATFULL
TI Heterovesicular liposomes
IN Kim, Sinil, Solana Beach, CA, United States
PA DepoTech Corporation, La Jolla, CA, United States (U.S. corporation)
PI US 5422120 950606
AI US 93-78701 930616 (8)
RLI Continuation-in-part of Ser. No. US 88-196590, filed on 30 May 1988, now abandoned which is a continuation-in-part of Ser. No. US 90-496846, filed on 21 Mar 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Spensley Horn Jubas & Lubitz
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 925
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are heterovesicular liposomes containing substances of different biologically active compositions each encapsulated in separate chambers of the liposomes, having defined size distribution, adjustable average size, adjustable internal chamber size and number, methods of making them, and treatment of patients with them.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 23 OF 60 USPATFULL
AN 95:40928 USPATFULL

TI N-terminus modified analogs of LHRH
IN Haviv, Fortuna, Deerfield, IL, United States
Fitzpatrick, Timothy D., Boulder, CO, United States
Swenson, Rolf E., Grayslake, IL, United States
Nichols, Charles J., Greendale, WI, United States
Mort, Nicholas A., Waukegan, IL, United States
PA Tap Pharmaceuticals Inc., Deerfield, IL, United States (U.S. corporation)
PI US 5413990 950509
AI US 93-103022 930806 (8)
DT Utility
EXNAM Primary Examiner: Warden, Jill A.; Assistant Examiner: Huff, Sheela J.
LREP Janssen, Jerry F.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1042
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Decapaptides substituted on the N-terminal nitrogen atom by acyl groups are potent antagonists of LHRH and are useful for suppressing the levels of sex hormones in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 24 OF 60 USPATFULL
AN 94:97559 USPATFULL
TI Methods of treating or preventing breast or endometrial cancer with low dose non-masculinizing androgenic compounds
IN Labrie, Fernand, Quebec, Canada
PA Endorecherche, Inc., Canada (non-U.S. corporation)
PI US 5362720 941108
AI US 93-15083 930208 (8)
RLI Continuation of Ser. No. US 91-724532, filed on 28 Jun 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Ostrolenk, Faber, Gerb & Soffen
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1452
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and endometriosis in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 25 OF 60 USPATFULL
AN 94:55332 USPATFULL
TI [Gln']-luteinizing hormone releasing hormone conjugate of tetanus vaccine and its uses
IN Ladd, Anna E., New York, NY, United States

Thau, Rosemarie B., New York, NY, United States
Tsong, Yun-Yen, North Caldwell, NJ, United States
PA The Population Council, New York, NY, United States (U.S. corporation)
PI US 5324512 940628
AI US 90-634034 901226 (7)
DT Utility
EXNAM Primary Examiner: Kim, Kay K.
LREP Brumbaugh, Graves, Donohue & Raymond
CLMN Number of Claims: 15
ECL Exemplary Claim: 8
DRWN 25 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 1192
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present prevention provides an effective, fast acting method of vaccination useful in suppressing gonadotropic hormone release. The vaccine utilizes LHRH conjugated at its amino terminus to a protein carrier and can be mixed with either adjuvants or detergents in order to provide an effect vaccine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 26 OF 60 USPATFULL
AN 94:19954 USPATFULL
TI Manufacture of water-swellable hydrophilic articles and drug delivery devices
IN Moro, Daniel G., Randolph, NJ, United States
Kuzma, Petr, Monmouth Junction, NJ, United States
Quandt, Harry, North Middletown, NJ, United States
PA Hydro Med Sciences, a Division of National Patent Development Corporation, New York, NY, United States (U.S. corporation)
PI US 5292515 940308
AI US 93-41523 930331 (8)
RLI Continuation of Ser. No. US 90-589957, filed on 28 Sep 1990, now abandoned
PRAI EP 92-300394 921005
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Bawa, Raj
LREP Howson and Howson
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 1389
AB A method of preparing a hydrophilic plastic cartridge by centrifugally cang polymerizable hydrophilic material in a rotating polymerization tube whose longitudinal axis is maintained parallel to the ground. The speed of rotation causes radial outward displacement of the polymerizable material which upon assuming a predetermined shape within the rotating tube is then polymerized to the predetermined solid configuration. The resulting plastic cartridge is characterized by smooth, unscored internal and external cylindrical surfaces. The cartridges are used as a rate-limiting membrane in drug delivery devices. Sterilized kits containing a disposable needle/syringe or trocar-like instrument and the drug delivery device are used for subcutaneous implantation of the device in an animal body.

L135 ANSWER 27 OF 60 USPATFULL
AN 93:100501 USPATFULL

TI Preparation of homogeneous hydrogel copolymers
IN Kuzma, Petr, Monmouth Junction, NJ, United States
Moro, Daniel G., Randolph, NJ, United States
Quandt, Harry, North Middletown, NJ, United States
PA Hydro Med Science Division of National Patent Development Corp., New York, NY, United States (U.S. corporation)
PI US 5266325 931130
AI US 90-621346 901203 (7)
RLI Continuation-in-part of Ser. No. US 90-589957, filed on 28 Sep 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Bawa, Raj
LREP Howson and Howson
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 1583
AB A method is provided for the preparation of homogeneous copolymers having aredetermined equilibrium water content (EWC) value formed by the addition polymerization of a mixture of ethylenically unsaturated monomer A and ethylenically unsaturated monomer B, for example, 2-hydroxyethyl methacrylate and hydroxypropyl methacrylate. The method requires determining the EWC values of the hydrogel homopolymer of hydrophilic monomer A (homopolymer A) and the hydrogel homopolymer of hydrophilic monomer B (homopolymer B); determining the relationship of the EWC values of the homogeneous copolymers AB versus the chemical composition of said copolymers AB; selecting the targeted EWC value and determining the chemical composition of copolymer AB having the targeted EWC value; forming a polymerizable mixture of monomer A and monomer B in amounts sufficient to yield copolymer AB having the targeted EWC value; and effect the polymerization reaction to yield copolymer AB characterized by the targeted EWC value. A method is also provided for the preparation of a delivery device including a drug contained in the reservoir of the hydrogel of copolymer AB, said device being characterized by its capability of eluting or releasing the drug through the hydrogel membrane to a delivery environment at a predetermined rate. There is also disclosed a sterilized kit containing a trocar or hypodermic needle/syringe and the aforesaid drug delivery device having a cylindrical shape with a rounded or bullet-like extremity.

L135 ANSWER 28 OF 60 USPATFULL
AN 93:91746 USPATFULL
TI LHRH analogues with cytotoxic moieties at the sixth position
IN Schally, Andrew V., Metarie, LA, United States
Bajusz, Sandor, Budapest, Hungary
PA The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5258492 931102
AI US 91-710515 910603 (7)
DCD 20091215
RLI Continuation of Ser. No. US 89-404667, filed on 7 Sep 1989, now abandoned which is a continuation-in-part of Ser. No. US 88-260994, filed on 21 Oct 1988, now abandoned
DT Utility
EXNAM Primary Examiner: Cashion, Jr., Merrell C.; Assistant Examiner: Wessendorf, T.
LREP Behr, Omri M.; McDonald, Matthew J.

CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1574
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention deals with LHRH analogues which contain cytotoxic moieties and have influence on the release of gonadotropins from the pituitary gland of mammals, including humans. The compounds of this invention are represented by the formula:

X--R.sup.1 --R.sup.2 --R.sup.3 -Ser-R.sup.5 --R.sup.6 (Q)-Leu-Arg-Pro-R.sup.10 --NH.sub.2

wherein

R.sup.1 is pGlu, Pro, D-Nal(2), or D-Phe(4Cl),

R.sup.2 is His or D-Phe(4Cl),

R.sup.3 is Trp, D-Trp or D-Pal(3),

R.sup.5 is Tyr or Arg,

R.sup.6 is D-Phe or R*.sup.6, where R*.sup.6 is D-Orn, D-Lys or D-Phe(NH.sub.2),

R.sup.10 is Gly or D-Ala,

X is hydrogen, a lower alkanoyl group of 2-5 carbon atoms or carbamyl,

Q is bis-(2-chloroethyl)amino group provided that R.sup.6 is D-Phe,

where R.sup.6 is R*.sup.6,

Q is a complexed metal-containing acyl group having the formula: ##STR1## wherein Q' is Pt(Y).sub.2, where Y is an anion derived from a pharmaceutically acceptable acid,

A is a diaminoacyl group having the formula ##STR2## where m is 0 or 1,

n and p are 0-10,

o is 1-10,

Q" is a non-platinum-group metal, either a main-group metal such as gallium, germanium, and tin, or a transition metal such as titanium, vanadium, iron, copper, cobalt, gold, nickel, cadmium and zinc,

B is a aralkylidene, heteroaralkylidene, cycloalkylidene or heterocycloalkylidene group containing oxygen anion or carboxylate anion at position 2 or 3, and pharmaceutically acceptable salts thereof and methods of use pertaining these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 29 OF 60 USPATFULL
AN 93:25009 USPATFULL
TI LHRH antagonists
IN Schally, Andrew V., Metarie, LA, United States
Bajusz, Sandor, New Orleans, LA, United States
PA The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5198533 930330
AI US 88-197153 880523 (7)
DCD 20060124
RLI Continuation-in-part of Ser. No. US 87-74126, filed on 17 Jul 1987, now abandoned
DT Utility
EXNAM Primary Examiner: Cashion, Jr., Merrell C.; Assistant Examiner: Wessendof, T. D.
LREP Behr, Omri M.; McDonald, Matthew J.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 927
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention deals with LHRH antagonists which possess improved water solubility and while having the high antagonist potency of the basic peptides, are free of the edematogenic effects. These compounds are highly potent in inhibiting the release of gonadotropins from the pituitary gland in mammals, including humans.

The compounds of this invention are represented by the formula

X--R.sup.1 --R.sup.2 --R.sup.3 --Ser--Tyr--R.sup.6 --Leu--Arg--Pro--R.sup.10 --NH.sub.2

wherein

X is an acyl group derived from straight or branched chain aliphatic or alicyclic carboxylic acids having from 1 to 7 carbon atoms, or H.sub.2 N--CO,

R.sup.1 is D-- or L--Pro, D-- or L--.DELTA..sup.3 --Pro, D--Phe, D--Phe(4--H1), D--Ser, D--Thr, D--Ala, D--Nal(1) or D--Nal (2),

R.sup.2 is D--Phe or D--Phe(4--C1)

R.sup.3 is D--Trp, D--Phe, D--Pal(3), D--Nal(1) or D--Nal(2),

R.sup.6 is D--Cit, D--Hci, D--Cit(Q) or D--Hci(Q) and

R.sup.10 is Gly or D--Ala

where Q is lower alkyl of 1-3 carbon atoms and H1 is fluoro, chloro or bromo, and the pharmaceutically acceptable acid addition salts thereof and methods of use pertaining to these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 30 OF 60 USPATFULL
AN 92:103148 USPATFULL
TI LHRH antagonists
IN Janaky, Tamas, Szeged, Hungary

Juhasz, Atilla, Budapest, Hungary
Schally, Andrew V., Metairie, LA, United States
PA The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5171835 921215
AI US 91-647786 910130 (7)
RLI Continuation-in-part of Ser. No. US 89-404667, filed on 7 Sep 1989, now abandoned which is a continuation-in-part of Ser. No. US 88-260994, filed on 21 Oct 1988, now abandoned
DT Utility
EXNAM Primary Examiner: Cashion, Jr., Merrell C.; Assistant Examiner: Wessendorf, T. D.
LREP Behr, Omri M.; McDonald, Matthew J.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1187
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein are analogues of the luteinizing hormone-releasing hormone (LH-RH), which are potent antagonists of LH-RH. These peptides inhibit the release of gonadotropins from the pituitary in mammals, including humans and possess antitumor activity.

Formula I represents peptides which are within the scope of this invention:

X--R.sup.1 --R.sup.2 --R.sup.3 --Ser--R.sup.5 --R.sup.6 (AY.sub.2)--Leu--Arg--Pro--D--Ala--NH.sub.2 I

and the pharmaceutically acceptable salts thereof, wherein

R.sup.1 is D-Phe, D-Phe(4Cl), D-Nal(1) or D-Nal(2),

R.sup.2 is D-Phe or D-Phe(4HI),

R.sup.3 is D-Trp, D-Phe, D-Phe(4HI), D-Nal(1), D-Nal(2) or D-Pal(3),

R.sup.5 is Tyr or Arg,

R.sup.6 is D-Lys or D-Orn,

HI is fluoro, chloro or bromo

X is a lower alkanoyl group of 2-5 carbon atoms,

A is a diaminoacyl residue having the formula ##STR1## where m is 0 or 1,

n is 0 or 1,

Y is Y.sup.1 or Y.sup.2, wherein

Y.sup.1 is an acyl group derived from straight or branched chain aliphatic, alicyclic carboxylic acids having from 3 to 12 carbon atoms or aromatic carboxylic acid of 6 or 10 ring carbon atoms,

Y.sup.2 is carbamoyl or alkyl-substituted carbamoyl group having the formula

H--(CH.sub.2).sub.n --NH--CO-- III

where n is 0-3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 31 OF 60 USPATFULL
AN 92:57503 USPATFULL
TI Continuous delivery of luteinizing hormone releasing hormone compositions in combination with sex steroid delivery for use in treating benign ovarian secretory disorders
IN Crowley, Jr., William F., Newtonville, MA, United States
PA The General Hospital Corporation, Boston, MA, United States (U.S. corporation)
PI US 5130137 920714
AI US 89-391278 890809 (7)
DCD 20050809
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Webman, E. J.
LREP Sterne, Kessler, Goldstein & Fox
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to a delivery system and a method useful for the treatment of benign ovarian secretory disorders in female mammals by administering an LHRH composition. The method comprises administering during the entire follicular phase of the menstrual cycle, beginning at the time of menses, an LHRH composition and sufficient levels of an estrogenic steriod to counteract the possibility of side effects which may develop during prolonged therapy with LHRH. Following the follicular phase, at the beginning of the luteal phase, and for the entire course of the luteal phase, the LHRH/estrogenic steroid combination administered during the follicular phase, in combination with a physiological amount of progestational steroid, is administered.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 32 OF 60 USPATFULL
AN 92:42743 USPATFULL
TI LHRH preparations for intranasal administration
IN Anik, Shabbir T., Palo Alto, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5116817 920526
AI US 90-587494 900920 (7)
RLI Continuation of Ser. No. US 87-20419, filed on 20 Jan 1987, now abandoned which is a continuation of Ser. No. US 85-741312, filed on 4 Jun 1985, now abandoned which is a continuation-in-part of Ser. No. US 82-448548, filed on 10 Dec 1982, now abandoned
DT Utility
EXNAM Primary Examiner: Griffin, Ronald W.
LREP Moran, Tom M.; Freyberg, Derek P.; Schmonsees, William
CLMN Number of Claims: 11
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 689
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel nasal composition comprising a nona- or decapeptide having LHRH agonist or antagonist activity and a surfactant which is a bile acid or a pharmaceutically acceptable salt thereof in a buffered aqueous solution.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 33 OF 60 USPATFULL
AN 92:1720 USPATFULL
TI Quarternary pyridinium salts
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5079366 920107
AI US 89-417037 891004 (7)
RLI Division of Ser. No. US 87-35648, filed on 7 Apr 1987, now patented, Pat. No. US 4888427
DT Utility
EXNAM Primary Examiner: Richter, Johann
LREP Baumeister, Mary K.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2756
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel amino acids and peptides containing them which comprise a dihydropyridine.revreaction.pyridinium salt-type redox system and which provide site-specific and sustained delivery of pharmacologically active peptides to the brain. These new amino acids contain a redox system appended directly or via an alkylene bridge to the carbon atom adjacent to the carboxyl carbon and may be incorporated into a peptide chain at a variety of positions, including non-terminal positions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 34 OF 60 USPATFULL
AN 91:102290 USPATFULL
TI Therapeutic decapeptides
IN Coy, David H., New Orleans, LA, United States
Moreau, Jacques-Pierre, Upton, MA, United States
PA Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5073624 911217
AI US 89-352140 890515 (7)
DCD 20060912
RLI Continuation-in-part of Ser. No. US 87-65765, filed on 23 Jun 1987, now patented, Pat. No. US 4866160 which is a continuation-in-part of Ser. No. US 86-879338, filed on 27 Jun 1986, now abandoned which is a continuation-in-part of Ser. No. US 85-798239, filed on 14 Nov 1985, now abandoned which is a continuation-in-part of Ser. No. US 85-721330, filed on 9 Apr 1985, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Fish & Richardson

CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 370
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A decapeptide of the formula: N-AC-A.sup.1 -A.sup.2 -A.sup.3 -Ser-A-.sup.4 -A.sup.5 -A.sup.6 -A.sup.7 -A.sup.8 -A.sup.9, wherein each A.sup.1, A.sup.2, and A.sup.3, independently, is D-.beta.-Nal, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, or C.sub.1-3 alkyl), D-benzothienyl (2)-Ala, or D-benzothienyl (1)-Ala; A.sup.4 is p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, or C.sub.1-3 alkyl), Tyr, Lys, Arg, Leu, Trp, or Nal; A.sup.5 is D-Lys, D-Tyr, D-Arg, D-Phe, D-.beta.-Nal, D-Trp, D-homo-Arg, D-diethyl-homo-Arg, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, or C.sub.1-3 alkyl), or D-Lys-.epsilon.-NH-R (where R is H, a branched or straight chain C.sub.1 -C.sub.10 alkyl group, or an aryl group); A.sub.6 is Leu, .beta.-Nal, p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, C.sub.2 F.sub.5, C.sub.1-3 alkyl), or Trp; A.sup.7 is Arg, Lys, or Lys .epsilon.-NH-R (where R is H, a branched or straight chain C.sub.1 -C.sub.6 alkyl group, or an aryl group); A.sub.8 is Pro; and A.sup.9 is D-Ala, D-Ala-NH.sub.2, Ala-NH.sub.2, aminoisobutyric acid amide, or Gly-NH.sub.2 ; provided that at least one of A.sup.2 or A.sup.3 must be D-Phe or D-Tyr, and provided further that when A.sup.4 is Lys or Arg, A.sup.5 must not be D-Arg, D-Lys, D-homo-Arg, D-diethyl-homo-Arg, or D-Lys-.epsilon.-NH-R, or a pharmaceutically acceptable salt thereof.

The invention also features a method of treating T-cell-deficient patients, e.g., those suffering from Acquired Immune Dificiency Syndrome, by administering a therapeutically effective amount of an LH-RH antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 35 OF 60 USPATFULL
AN 91:52370 USPATFULL
TI Delivery systems for the controlled administration of LHRH analogs
IN Sanders, Lynda M., Palo Alto, CA, United States
Burns, Jr., Ramon A., San Jose, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5028430 910702
AI US 87-47738 870508 (7)
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Moran, Tom M.; Johnson, Lester E.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 890
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An implantable polymeric delivery system for the controlled and continuous administration of an LHRH agonist which comprises a silicone elastomer matrix in which is dispersed about 30 to about 42 weight percent of water-soluble particulate phase containing an LHRH analog or a pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 36 OF 60 USPATFULL
AN 91:24720 USPATFULL
TI Therapeutic decapeptides
IN Coy, David H., New Orleans, LA, United States
Moreau, Jacques-Pierre, Upton, MA, United States
PA The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 5003011 910326
AI US 89-421245 891013 (7)
DCD 20060912
RLI Continuation-in-part of Ser. No. US 89-352140, filed on 15 May 1989, now abandoned which is a continuation of Ser. No. US 87-65765, filed on 19 Jun 1987, now patented, Pat. No. US 4866160 which is a continuation-in-part of Ser. No. US 86-879338, filed on 27 Jun 1986, now abandoned which is a continuation-in-part of Ser. No. US 85-798239, filed on 14 Nov 1985, now abandoned which is a continuation-in-part of Ser. No. US 85-721330, filed on 9 Apr 1985, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Fish & Richardson
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 746
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A decapeptide of the formula:

N-Ac-A.sup.1 -A.sup.2 -A.sup.3 -SER.sup.4 -A.sup.5 -A.sup.6 -A.sup.7 -A.sup.8 -A.sup.9 -A.sup.10,

wherein each A.sup.1, A.sup.2, and A.sup.3, independently, is D-.beta.-Nal, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, or C.sub.1-3 alkyl); A.sup.5 is p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, or C.sub.1-3 alkyl); A.sup.6 is D-Lys, D-Arg, .beta.-Nal, D-.beta.-Nal, D-Trp, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, or C.sub.1-3 alkyl) or D-lys-.epsilon.-NH-R (where R is H, a branched or straight chain or cyclo C.sub.1 -C.sub.10 alkyl group, or an aryl group); A.sup.7 is p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, C.sub.2 F.sub.5, or C.sub.1-3 alkyl), cyclohexyala, or Trp; A.sup.8 is Arg, Lys, or Lys-.epsilon.-NH-R (where R is H, a branched or straight chain or cyclo C.sub.1 -C.sub.10 alkyl group, or an aryl croup); A.sup.9 is Pro; and A.sup.10 is D-Ala-NH.sub.2, Gly-NH.sub.2, D-Ser, or D-Ser-NH.sub.2 ; provided that at least one of A.sup.2 or A.sup.3 must be D-Phe or D-Tyr; and further provided that one or both of A.sup.6 and A.sup.8 must be the following: A.sup.6 must be D-Lys-.epsilon.-NH-R (where R is H, a branched or straight chain or cyclo C.sub.1 -C.sub.10 alkyl group, or an aryl group); A.sup.8 must be Lys-.epsilon.-NH-R (where R is H, a branched or straight chain or cyclo C.sub.1 -C.sub.10 alkyl group, or an aryl group), or a pharmaceuticaly acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 37 OF 60 USPATFULL
AN 90:74952 USPATFULL
TI Delayed/sustained release of macromolecules

IN Sanders, Lynda M., Palo Alto, CA, United States
Domb, Abraham, Brookline, MA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4959217 900925
AI US 86-866042 860522 (6)
DT Utility
EXNAM Primary Examiner: Page, Thurman K.
LREP Lowin, David A.; Dhuey, John A.
CLMN Number of Claims: 48
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1570
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention concerns novel, delayed/sustained release devices and compositions, including methods of their manufacture and use. The compositions include macromolecules, particularly polypeptide pharmaceuticals, and an initially partially-hydrated, non-biodegradable, hydrogel rate-limiting membrane.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 38 OF 60 USPATFULL
AN 89:100700 USPATFULL
TI Amino acids containing dihydropyridine ring systems for site-specific delivery of peptides to the brain
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 4888427 891219
AI US 87-35648 870407 (7)
DT Utility
EXNAM Primary Examiner: Fan, Jane T.
LREP Baumeister, Mary K.; Clarke, Dennis P.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2686
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel amino acids and peptides containing them which comprise a dihydropyridine.revreaction.pyridinium salt-type redox system and which provide site-specific and sustained delivery of pharmacologically active peptides to the brain. These new amino acids contain a redox system appended directly or via an alkylene bridge to the carbon atom adjacent to the carboxyl carbon and may be incorporated into a peptide chain at a variety of positions, including non-terminal positions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 39 OF 60 USPATFULL
AN 89:76573 USPATFULL
TI Therapeutic decapeptides
IN Coy, David H., New Orleans, LA, United States
Moreau, Jacques-Pierre, Upton, MA, United States
PA The Administrators of the Tulane Educational Fund, New Orleans, LA, United States (U.S. corporation)
PI US 4866160 890912
AI US 87-65765 870623 (7)
RLI Continuation-in-part of Ser. No. US 86-879338, filed on 27 Jun

1986, now abandoned And a continuation-in-part of Ser. No. US 85-798239, filed on 14 Nov 1985, now abandoned which is a continuation-in-part of Ser. No. US 85-721330, filed on 9 Apr 1985, now abandoned
DT Utility
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Nutter, Nathan M.
LREP Clark, Paul T.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 366
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A decapeptide of the formula:

N-Ac-A.sup.1 -A.sup.2 -A.sup.3 -Ser-A.sup.4 -A.sup.5 -A.sup.6 -A.sup.7 -A.sup.8 -A.sup.9, wherein each A.sup.1, A.sup.2, and A.sup.3, independently, is D-.beta.-Nal, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, or C.sub.1-3 alkyl), D-Trp, D-benzothienyl (2)-Ala, or D-benzothienyl (1)-Ala; A.sup.4 is p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, or C.sub.1-3 alkyl), Tyr, Lys, Arg, Leu, Trp, or Nal; A.sup.5 is D-Lys, D-Tyr, D-Arg, D-Phe, D-.beta.-Nal, D-Trp, D-homo-Arg, D-diethyl-homo-Arg, D-p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, or C.sub.1-3 alkyl), or D-Lys-.epsilon.-NH-R (where R is H, a branched or straight chain C.sub.1 -C.sub.10 alkyl group, or an aryl group); A.sub.6 is Leu, .beta.-Nal, p-X-Phe (where X is halogen, H, NH.sub.2, NO.sub.2, OH, C.sub.2 F.sub.5, C.sub.1-3 alkyl), or Trp; A.sup.7 is Arg, Lys, or Lys .epsilon.-NH-R (where R is H, a branched or straight chain C.sub.1 -C.sub.6 alkyl group, or an aryl group); A.sub.8 is Pro; and A.sup.9 is D-Ala, D-Ala-NH.sub.2, Ala-NH.sub.2, aminoisobutyric acid amide, or Gly-NH.sub.2 ; provided that at least one of A.sup.2 or A.sup.3 must be D-Phe or D-Tyr, and provided further that when A.sup.4 is Lys or Arg, A.sup.5 must not be D-Arg, D-Lys, D-homo-Arg, D-diethyl-homo-Arg, or D-Lys-.epsilon.-NH-R, or a pharmaceutically acceptable salt thereof.

The invention also features a method of treating T-cell-deficient patients, e.g., those suffering from Acquired Immune Deficiency Syndrome, by administering a therapeutically effective amount of an LH-RH antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 40 OF 60 USPATFULL
AN 89:60852 USPATFULL
TI LHRH antagonist analogs having low histamine-release activity
IN Roeske, Roger W., Indianapolis, IN, United States
PA Indiana University Foundation, Bloomington, IN, United States (U.S. corporation)
PI US 4851385 890725
AI US 87-73929 870715 (7)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Kirkland & Ellis
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 498

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Antagonist analogs of luteinizing hormone-releasing hormone (LHRH) having N-alkylated basic amino acid residues at the 8 position, 8 and 6 positions, 8 and 5 positions, and 8, 6 and 5 positions, having high antiovulatory activity and low histamine release activity, and their use in regulating the release of gonadatropic hormones from the pituitary gland of mannals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 41 OF 60 USPATFULL

AN 89:7543 USPATFULL

TI Nonapeptide and decapeptide analogs of LHRH useful as LHRH antagonists

IN Nestor, Jr., John J., San Jose, CA, United States
Vickery, Brian H., Saratoga, CA, United States

PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)

PI US 4801577 890131

AI US 87-10923 870205 (7)

DT Utility

EXNAM Primary Examiner: Foelak, Morton; Assistant Examiner: Chan, Christina

LREP Toth, Liza K.; Moran, Tom M.; Krubiner, Alan M.

CLMN Number of Claims: 41

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1729

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Synthetic nona- and decapeptide LHRH antagonist analogs are disclosed, having a sterically hindered guanidino-substituted arginyl or homoarginyl residue at position 8, with no arginyl substituent at position 6.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 42 OF 60 USPATFULL

AN 88:77512 USPATFULL

TI 17 a .beta.-hydroxy-7 .alpha.-methyl-d-homo-19-norandrost-4,16-diene-3-one and the 17-esters thereof: methods of preparation and uses

IN Tanabe, Masato, Palo Alto, CA, United States
Crowe, David F., Yreka, CA, United States
Detre, George, San Jose, CA, United States
Peters, Richard H., San Jose, CA, United States
Avery, Mitchell A.g34, Palo Alto, CA, United States

PA SRI International, Menlo Park, CA, United States (U.S. corporation)

PI US 4788218 881129

AI US 86-856386 860428 (6)

RLI Continuation-in-part of Ser. No. US 84-612415, filed on 21 May 1984, now abandoned

DT Utility

EXNAM Primary Examiner: Shippen, Michael L.

LREP Ciotti & Murashige, Irell & Manella

CLMN Number of Claims: 21

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1273

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel compounds having the general formula: ##STR1## wherein: R.sup.1 is hydrogen or an acyl substituent of the formula:

--(C.dbd.O)--R.sup.2

wherein:

R.sup.2 is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkylene, haloalkyl, aryl, haloaryl or arylalkylene are described. These compounds have both gonadotropic and antigonadotropic properties depending upon the dosage level, and are therefore useful in therapy in the control of male fertility in mammals, particularly in human beings. These compounds combine gonadotropic, antigonadotropic and androgenic properties in the same compound. Their use with LHRH antagonists on male fertility control is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 43 OF 60 USPATFULL
AN 88:50184 USPATFULL
TI Continuous delivery of luteinizing hormone releasing hormone compositions in combination with sex steroid delivery for use as a contraceptive
IN Crowley, Jr., William F., Newtonville, MA, United States
PA The General Hospital Corporation, Boston, MA, United States (U.S. corporation)
PI US 4762717 880809
AI US 86-842643 860321 (6)
DT Utility
EXNAM Primary Examiner: Page, Thurman K.
LREP Saidman, Sterne, Kessler & Goldstein
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 437
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to a delivery system and a method useful for preventing pregnancy in female mammals by administering an LHRH composition. The method comprises administering during the entire follicular phase of the menstrual cycle, beginning at the time of menses, an LHRH composition and sufficient levels of an estrogenic steroid to counteract the possibility of side effects which may develop during prolonged therepy with LHRH. Following the follicular phase, at the beginning of the luteal phase, and for the entire course of the luteal phase, the LHRH/estrogenic steroid combination administered during the follicular phase, in combination with a physiological amount of progestational steroid, is administered.

The delivery system comprises means for administering the LHRH composition, estrogenic steroid and progestational steroid.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 44 OF 60 USPATFULL
AN 87:77969 USPATFULL
TI Orally active LHRH analogs
IN Almquist, Ronald G., Palo Alto, CA, United States
Olsen, Cris M., Felton, CA, United States

PA SRI International, Menlo Park, CA, United States (U.S. corporation)
PI US 4705778 871110
AI US 85-790031 851022 (6)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Ciotti & Murashige, Irell & Manella
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Incorporation of a ketomethylene or a hydroxyethylene group in place of the amide linking group between the Pro.sup.9 and Gly.sup.10 residues of LHRH and its analogs improves the oral activity of LHRH or its analogs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 45 OF 60 USPATFULL
AN 87:61999 USPATFULL
TI Nona and decapeptide analogs of LHRH useful as LHRH antagonists
IN Nestor, Jr., John J., San Jose, CA, United States
Vickery, Brian, Cupertino, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4690916 870901
AI US 84-671153 841113 (6)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Toth, Liza K.; Moran, Tom M.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 961
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Synthetic nonapeptide and decapeptide LHRH antagonist analogues having a halo lower alkyl guanadino-substituted amino acyl residue at position six are disclosed herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 46 OF 60 USPATFULL
AN 87:48858 USPATFULL
TI Method for the treatment of LHRH diseases and conditions
IN Ho, Chih Y., Lansdale, PA, United States
PA McNeilab, Inc., Fort Washington, PA, United States (U.S. corporation)
PI US 4678784 870707
AI US 85-784963 851007 (6)
DCD 20030506
RLI Continuation-in-part of Ser. No. US 84-599095, filed on 11 Apr 1984, now patented, Pat. No. US 4547497 And a continuation-in-part of Ser. No. US 85-721723, filed on 10 Apr 1985, now patented, Pat. No. US 4587244
DT Utility
EXNAM Primary Examiner: Hollrah, Glennon H.; Assistant Examiner: Dinner, D. L.
LREP Lambert, Benjamin F.
CLMN Number of Claims: 5

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 633
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Fused tetracyclic benzodiazepines of the formula (I): ##STR1## where R.sup.1 is a cyclic amine such as 1-piperazine and R.sup.2 is H or a substituent as defined herein are useful as LHRH antagonizing agents. Also, methods for their synthesis, intermediates used in such synthesis, methods for use as medicaments and pharmaceutical compositions are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 47 OF 60 USPATFULL
AN 87:36194 USPATFULL
TI Nonapeptide and decapeptide analogs of LHRH, useful as LHRH antagonists
IN Nestor, Jr., John J., San Jose, CA, United States
Vickery, Brian H., Saratoga, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4667014 870519
AI US 83-495226 830520 (6)
DCD 20011106
RLI Continuation-in-part of Ser. No. US 83-472692, filed on 7 Mar 1983, now patented, Pat. No. US 4581169 which is a continuation-in-part of Ser. No. US 82-451671, filed on 21 Dec 1982, now patented, Pat. No. US 4481190
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Wise, Ellen J.; Moran, Tom M.; Krubiner, Alen M.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1756
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Synthetic nonpeptide and decapeptide LHRH antagonist analogs have a novel guanido-substituted, amidine, tertiary or quaternary amine water-soluble aminoacyl residue at position 6.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 48 OF 60 USPATFULL
AN 86:20084 USPATFULL
TI Nona-peptide and deca-peptide analogs of LHRH, useful as LHRH antagonists
IN Nestor, John J., San Jose, CA, United States
Vickery, Brian H., Cupertino, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4581169 860408
AI US 83-472692 830307 (6)
DCD 20011106
RLI Continuation-in-part of Ser. No. US 82-451671, filed on 21 Dec 1982, now patented, Pat. No. US 4481190
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.; Assistant Examiner: Moezie, F. T.
LREP Buckles, Ellen J.; Moran, Tom M.; Krubiner, Alan M.
CLMN Number of Claims: 1

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1185
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Synthetic nona-peptide and deca-peptide LHRH antagonist analogs have a novel guanido-substituted, amidine, tertiary or quaternary aminoacyl residue at position 6.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 49 OF 60 USPATFULL
AN 85:3167 USPATFULL
TI Contraceptive methods
IN Zimmerman, Ronald E., Danville, IN, United States
Burck, Philip J., Indianapolis, IN, United States
Jones, C. David, Indianapolis, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4493699 850115
AI US 82-366889 820408 (6)
DCD 19980428
DT Utility
EXNAM Primary Examiner: Rosenbaum, C. Fred; Assistant Examiner: Vinyard, Sherri E.
LREP Rowe, James L.; Whale, Arthur R.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 583
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Long chain alkyl and alkenyl sulfonates, sulfates and sulfoalkyl alkanoate salts, administered intravaginally for contraception.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 50 OF 60 USPATFULL
AN 84:62255 USPATFULL
TI Nonapeptide and decapeptide analogs of LHRH useful as LHRH antagonists
IN Nestor, John J., San Jose, CA, United States
Vickery, Brian H., Cupertino, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4481190 841106
AI US 82-451671 821221 (6)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.; Assistant Examiner: Moezie, F. T.
LREP Kanagy, James M.; Moran, Tom M.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1255
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nonapeptide and decapeptide analogs of LHRH which have the formula ##STR1## and the pharmaceutically acceptable salts thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 51 OF 60 USPATFULL
AN 84:49793 USPATFULL
TI Contraceptive device
IN Zimmerman, Ronald E., Danville, IN, United States
Burck, Philip J., Indianapolis, IN, United States
Dunn, Richard L., Birmingham, AL, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4469671 840904
AI US 83-468436 830222 (6)
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L.; Whale, Arthur R.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 637
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A contraceptive device for intravaginal use comprising a bioinsoluble, biocompatible polyurethane and an acrosin inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 52 OF 60 USPATFULL
AN 84:29965 USPATFULL
TI Means and method for administering medicinals
IN Harman, Sherman M., 9302 Michaels Way, Ellicott City, MD, United States 21043
PI US 4451253 840529
AI US 82-427136 820929 (6)
RLI Continuation-in-part of Ser. No. US 80-217780, filed on 18 Dec 1980, now abandoned
DT Utility
EXNAM Primary Examiner: Yasko, John D.
LREP Temko, Charles E.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 377
AB A device for administering elongate medicinal pellets in subcutaneous applications. The device includes a hand-held guide element including a hollow barrel enclosing a sliding member having a needle locking means at one end thereof. A disposable cartridge element includes a hollow needle containing a pellet to be implanted and an obturator of length somewhat greater than that of the needle. In use, the cartridge element is engaged at an end thereof with the guide element. The free end of the needle is inserted into the subcutaneous fat of the patient, and the sliding member is moved in an opposite direction to withdraw the needle into the hollow barrel. During this movement, the obturator is maintained relatively stationary by engaging an abutment on the guide element, at one end thereof, the opposite end of the obturator engaging an end of the pellet, so that as the needle is withdrawn, the pellet remains in implanted position. A composite pellet having a core formed of a first ingredient, and a surrounding sleeve formed of a second ingredient is also disclosed, as is a method for making the pellets using a soluble inert core having first and second ingredients coated thereon.

L135 ANSWER 53 OF 60 USPATFULL
AN 84:8839 USPATFULL
TI LH-RH Antagonists
IN Coy, David H., 4319 Perrier St., New Orleans, LA, United States 70115
Shally, Andrew V., 5025 Kawanee Ave., Metairie, LA, United States 70002
PI US 4431635 840214
AI US 82-341137 820120 (6)
RLI Continuation-in-part of Ser. No. US 80-115249, filed on 2 Jun 1980, now patented, Pat. No. US 4317315
DT Utility
EXNAM Primary Examiner: Phillips, Delbert K.
LREP Wegner & Bretschneider
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 867
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein are peptide analogs of the luteinizing hormone releasing hormone (LH-RH) which are potent antagonists of LHRH. The analogs differ in structure from LH-RH by having different amino acid residues at positions 1, 2 and 6, and optionally at positions 3 and 10. Methods for preparing and using these analogs are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 54 OF 60 USPATFULL
AN 83:57530 USPATFULL
TI Nonapeptide and decapeptide analogs of LHRH, useful as LHRH antagonists
IN Nestor, John J., San Jose, CA, United States
Jones, Gordon H., Cupertino, CA, United States
Vickery, Brian H., Cupertino, CA, United States
PA Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 4419347 831206
AI US 82-366635 820408 (6)
DCD 19971118
RLI Continuation of Ser. No. US 80-194180, filed on 6 Oct 1980, now patented, Pat. No. US 4341767, issued on 27 Jul 1982
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Kanagy, James M.; Moran, Tom M.
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1298
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nonapeptide and decapeptide analogs of LHRH which have the formula ##STR1## and the pharmaceutically acceptable salts thereof, wherein: X is a D-alanyl residue wherein one hydrogen on C-3 is replaced by:

(a) a carbocyclic aryl-containing radical selected from the group consisting of phenyl substituted with three or more straight chain lower alkyl groups, naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl and benzhydryl; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydronaphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl, and adamantyl; or

(c) a heterocyclic aryl containing radical selected from the group consisting of radicals represented by the following structural formulas: ##STR2## wherein A" and A' are independently selected from the group consisting of hydrogen, lower alkyl, chlorine, and bromine, and G is selected from the group consisting of oxygen, nitrogen, and sulfur;

A is an aminoacyl residue selected from the group consisting of L-pyroglutamyl, D-pyroglutamyl, N-acyl-L-prolyl, N-acyl-D-prolyl, N-acyl-D-tryptophanyl, N-acyl-D-phenylalanyl, N-acyl-D-p-halophenylalanyl, and N-acyl-X wherein X is as defined previously;

B is an amino acyl residue selected from the group consisting of D-phenylalanyl, D-p-halophenylalanyl, 2,2-diphenylglycyl, and X wherein X is as defined previously;

C is an amino acyl residue selected from the group consisting of L-tryptophanyl, D-tryptophanyl, D-phenylalanyl and X wherein X is as defined above;

E is glycinamide or --NH--R.sup.1, wherein R.sup.1 is lower alkyl, cycloalkyl, fluoro lower alkyl or ##STR3## wherein R.sup.2 is hydrogen or lower alkyl;

are disclosed. These compounds are LHRH antagonists.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 55 OF 60 USPATFULL
AN 82:10022 USPATFULL
TI LH-RH Antagonists
IN Coy, David H., 4319 Perrier St., New Orleans, LA, United States 70115
Schally, Andrew V., 5025 Kawanee Ave., Metairie, LA, United States 70002
PI US 4317815 820302
AI US 80-155249 800602 (6)
PRAI CA 79-329643 790613
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 867
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein are peptide analogs of the luteinizing hormone releasing hormone (LH-RH) which are potent antagonist of LHRH. The analogs differ in structure from LH-RH by having different amino acid residues at positions 1, 2 and 6, and optionally at positions 3 and 10. Methods for preparing and using these analogs are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 56 OF 60 USPATFULL

AN 81:23334 USPATFULL
TI Contraceptive methods and compositions
IN Burck, Philip J., Indianapolis, IN, United States
Zimmerman, Ronald E., Danville, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4264578 810428
AI US 80-138394 800408 (6)
RLI Continuation-in-part of Ser. No. US 79-57931, filed on 16 Jul 1979, now abandoned which is a continuation of Ser. No. US 78-973252, filed on 26 Dec 1978, now abandoned
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L..; Whale, Arthur R.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 602
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Introduction of a pharmaceutically acceptable non-toxic cation salt of a sterol sulfate into the uterine lumen or vaginal cavity prevents conception. Potassium or pyridinium .beta.-sitosteryl sulfate is preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 57 OF 60 USPATFULL
AN 81:23333 USPATFULL
TI Contraceptive methods and compositions
IN Zimmerman, Ronald E., Danville, IN, United States
Burck, Philip J., Indianapolis, IN, United States
Jones, C. David, Indianapolis, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4264577 810428
AI US 80-138393 800408 (6)
RLI Continuation-in-part of Ser. No. US 79-63507, filed on 3 Aug 1979, now abandoned Continuation of Ser. No. US 78-973251, filed on 26 Dec 1978, now abandoned
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L.; Whale, Arthur R.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Introduction of a compound of the formula:

R--OSO.sub.3 --M

wherein R is:

(a) C.sub.11 -C.sub.30 straight chain alkyl or alkenyl;

(b) C.sub.10 -C.sub.30 branched chain alkyl or alkenyl, the .alpha.-carbon of which is not branched; or

(c) C.sub.13 -C.sub.30 branched chain alkyl or alkenyl, the .alpha.-carbon of which is branched,

and M is a pharmaceutically acceptable non-toxic cation; into the uterine lumen or vaginal cavity prevents conception. Sodium n-tetradecyl sulfate is preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 58 OF 60 USPATFULL
AN 81:23332 USPATFULL
TI Contraceptive methods and compositions
IN Zimmerman, Ronald E., Danville, IN, United States
Burck, Philip J., Indianapolis, IN, United States
Jones, C. David, Indianapolis, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4264576 810428
AI US 80-138376 800408 (6)
RLI Continuation-in-part of Ser. No. US 79-52713, filed on 28 Jun 1979, now abandoned which is a continuation of Ser. No. US 78-973253, filed on 26 Dec 1978, now abandoned
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L.; Whale, Arthur R.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 682
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Introduction of a pharmaceutically acceptable non-toxic cation salt of a sulfoalkyl alkanoate, for example, sodium sulfopropyl dodecanoate, into the uterine lumen or vaginal cavity prevents conception.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 59 OF 60 USPATFULL
AN 81:23331 USPATFULL
TI Contraceptive methods and compositions
IN Zimmerman, Ronald E., Danville, IN, United States
Burck, Philip J., Indianapolis, IN, United States
Jones, C. David, Indianapolis, IN, United States
Thakkar, Arvind L., Indianapolis, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4264575 810428
AI US 80-138375 800408 (6)
RLI Continuation-in-part of Ser. No. US 79-58040, filed on 16 Jul 1979, now abandoned which is a continuation of Ser. No. US 78-973205, filed on 26 Dec 1978, now abandoned
DT Utility
EXNAM Primary Examiner: Rose, Shep K.
LREP Rowe, James L.; Whale, Arthur R.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 510
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Introduction of a pharmaceutically acceptable non-toxic cation salt of a straight-chain or branched chain alkyl sulfonate having from 11 to 16 carbon atoms into the uterine lumen or vaginal cavity prevents conception. Sodium tetradecyl sulfonate is preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L135 ANSWER 60 OF 60 USPATFULL
AN 78:9993 USPATFULL
TI Biologically active amides
IN Beddell, Christopher Raymond, Ashford, England
Lowe, Lawrence Alfred, Swanley, England
Wilkinson, Samuel, Beckenham, England
PA Burroughs Wellcome Co., Research Triangle Park, NC, United States (U.S. corporation)
PI US 4075191 780221
AI US 75-625386 751024 (5)
PRAI GB 74-46167 741025
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Brown, Donald
CLMN Number of Claims: 6
ECL Exemplary Claim: 1,6
DRWN No Drawings
LN.CNT 740
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel peptide compounds of the formula

X.sup.1 --X.sup.2 --X.sup.3 --X.sup.4 --X.sup.5 --X.sup.6 --X.sup.7 --X.sup.8 --Pro--W

are provided together with their acid addition salts and their complexes with pharmaceutically acceptable metals. The compounds are LH-RH analogues and together with their salts and complexes exhibit LH-RH antagonist activity.

In the formula

X.sup.1 is selected from pyroglutamyl, a group V.sup.1 -Pro- where V.sup.1 is acyl, alkyloxycarbonyl or aralkyloxycarbonyl, and a group V.sup.2 --CO-- where V.sup.2 is cycloalkyl;

X.sup.2 is selected from histidyl and a direct bond;

X.sup.3 is selected from phenylalanyl optionally substituted in the benzene ring and tryptophyl;

X.sup.4 is selected from glycyl, seryl, alanyl (D- or L), D-leucyl and D-valyl;

X.sup.5 is phenylalanyl optionally substituted in the benzene ring;

X.sup.6 is selected from glycyl, alanyl (D- or L-), D-leucyl and D-valyl;

X.sup.7 is selected from phenylalanyl optionally substituted in the benzene ring and leucyl;

X.sup.8 is a direct bond when X.sup.2 is histidyl and is otherwise arginyl or homoarginyl; and

W is selected from glycine amide and a group --NR.sup.1 R.sup.2 where R.sup.1, R.sup.2 and the nitrogen atom together comprise a group selected from amino, N-alkylamino, N,N-dialkylamino, pyrrolidino, morpholino and 1-methyl-5-aminomethyltetrazolyl, the `alkyl` having from 1 to 4 carbon atoms and being optionally substituted by an hydroxyl group, provided that, when X.sup.1, X.sup.3, X.sup.4, X.sup.5, X.sup.7 and X.sup.8 are respectively pyroglutamyl, tryptophyl, seryl, tyrosyl, leucyl and arginyl, W is other than glycine amide or N-ethylamino when X.sup.6 is glycyl and is other than glycine amide when X.sup.6 is D-alanyl.

All references are to the L-amino acids and their radicals except in the case of glycine and unless otherwise stated.

Also provided are methods for the preparation of the peptides, salts and complexes, pharmaceutical formulations containing them and methods for the preparation of such formulations, and methods for the use of the peptides, salts and complexes in human and in veterinary medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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